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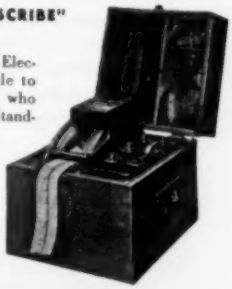

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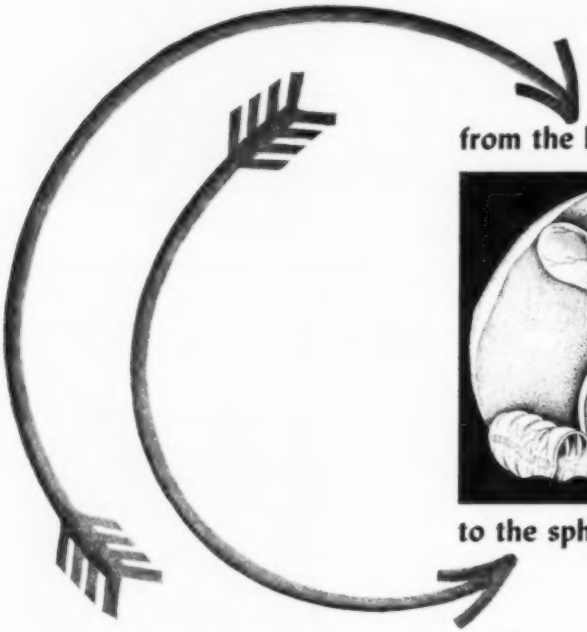
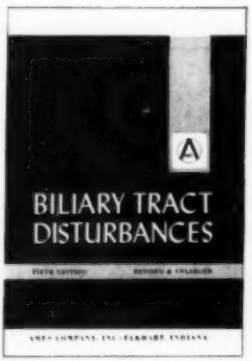


The area surveyed in the Fifth Edition of "Biliary Tract Disturbances," now available, is the entire, ramified biliary tree—its anatomic and physiologic background and the diagnosis and therapy of its disorders.

Physicians and surgeons acquainted with previous editions of this monograph will find the newly revised, enlarged and illustrated edition even more practical. The brochure concisely presents basic concepts of biliary tract disease, and reviews recent progress in the management of biliary disorders with hydrocholeretics and other measures. You may receive your copy on request from the Medical Department, Ames Company, Inc., Elkhart, Indiana.



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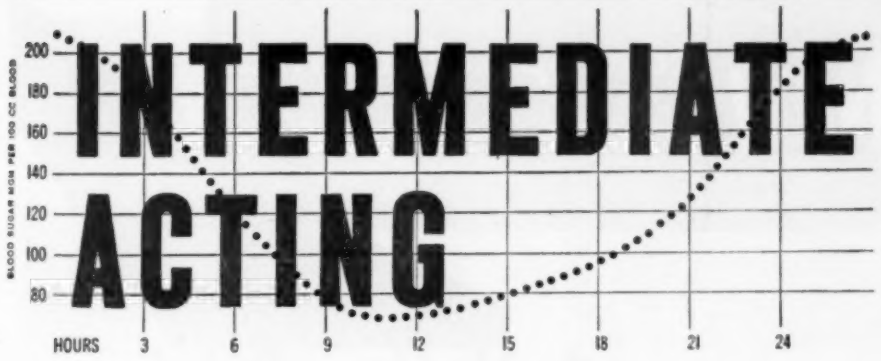

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In 10 cc. vials, U-40 and U-80.

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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New concept of control in nasal congestion

Antistine-Privine
NASAL SOLUTION

A combination of an Antihistaminic and Vasoconstrictor

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This new synergistic combination contains the effective antihistaminic, Antistine, to block the congestive action of histamine and the most potent vasoconstrictor, Privine, to shrink the nasal mucosa.

It has been established that "the decongestant action of Antistine-Privine on the allergic nasal mucosa in many instances appears to be more intense and prolonged than from either solution alone."[1]

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PRIVINE hydrochloride, 0.05% solution in 1 oz. dropper bottles for prescription; 0.1% solution reserved for office procedures, in 1 pint bottles only.

1. Friedlaender & Friedlaender: Amer. Pract. 2:643, June, 1948

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ANTISTINE (brand of antazoline); PRIVINE (brand of naphazoline) • Trade Marks Reg. U.S. Pat. Off. 2/1804M

Before Treatment (*9 days prior to Dihydrostreptomycin therapy*) *Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).*

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when the problem is
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a new approach to a group of common and difficult clinical problems

MONITAN is a palatable solution of sorbitan monooleate polyoxyethylene derivative.

MONITAN will efficiently emulsify fats, oils and fat-soluble substances for better absorption.

MONITAN is indicated in the treatment of conditions where excess quantities of fat are excreted (steatorrhea).

MONITAN is given orally.

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safe and effective reduction
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Clinical and experimental observations indicate that lipotropic factors [choline, methionine and inositol] . . . prevent or mitigate the deposition of cholesterol in the vascular walls of rabbits and chickens and seem to exert a decholesterolizing effect on atheromatous deposits in man, chickens and rabbits.

These findings suggest the therapeutic possibilities of lipotropic Methischol in the prevention and possible treatment of atherosclerosis.

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Suggested daily therapeutic dose of 3 tablespoonsful or 9 capsules contains:

*Choline Dihydrogen Citrate (Choline . . . 1 Gm.)**	*2.5 Gm.*
dl-Methionine	*1.0 Gm.*
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Liver Fractions from	*36.0 Gm. liver*
**present in syrup as 1.15 Gm. choline chloride*	

Supplied in bottles of 100, 250, 500 and 1000 capsules, and 16 oz. and one gallon syrup.

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combines major lipotropic agents for specific therapy in reparable liver damage . . . cirrhosis, fat infiltration, functional impairment, toxic hepatitis, infectious hepatitis.

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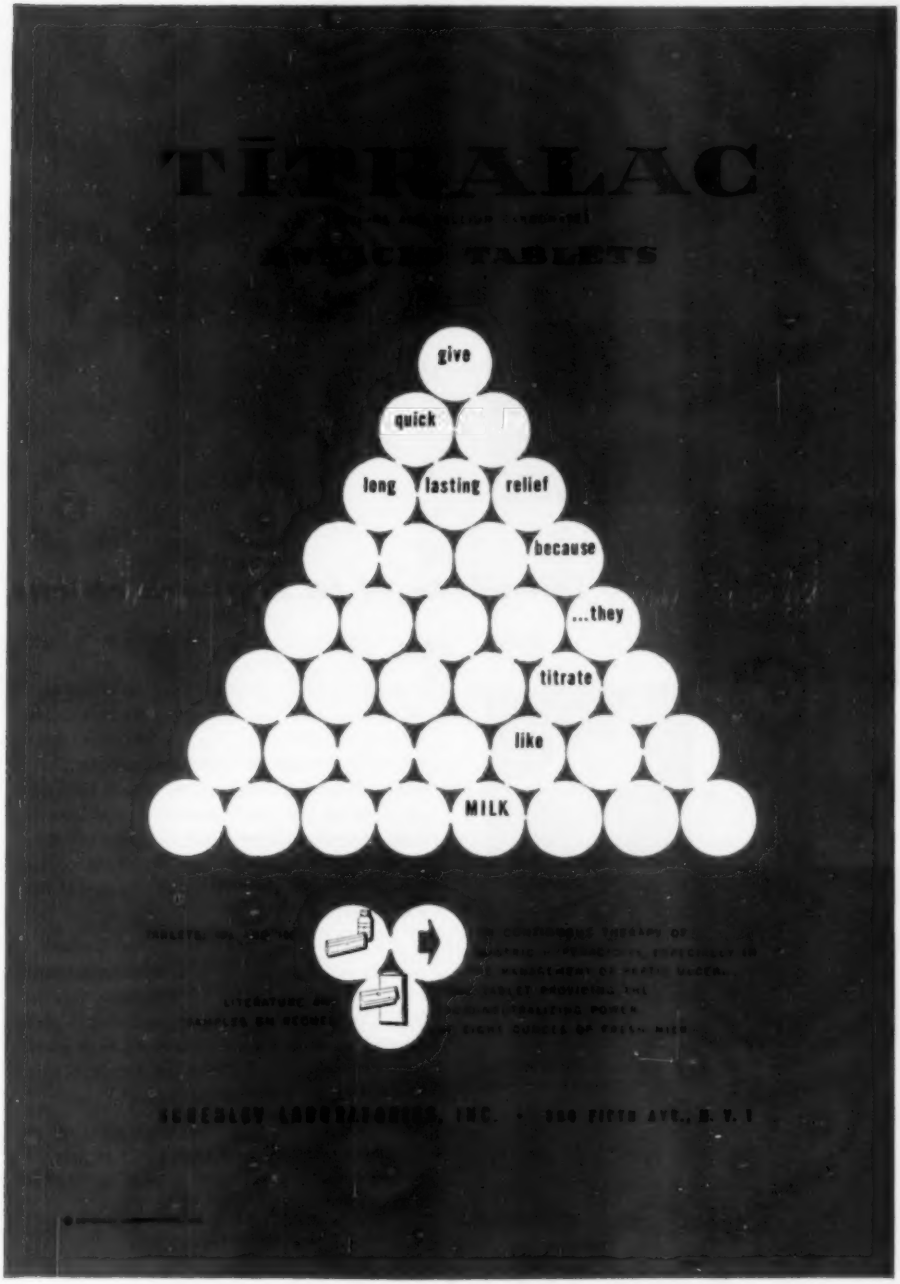
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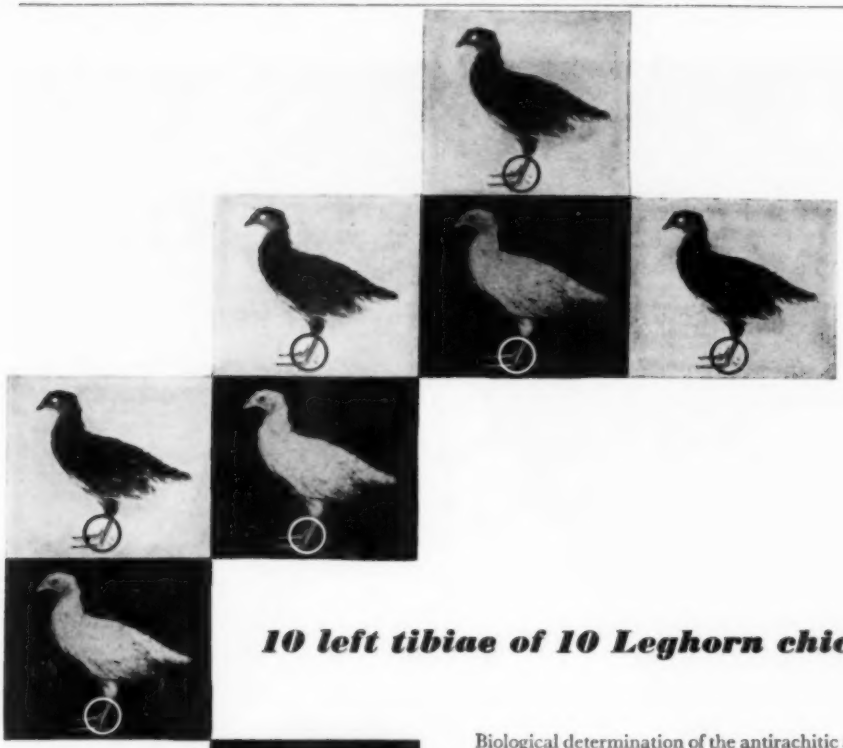

10 left tibiae of 10 Leghorn chicks

Biological determination of the antirachitic activity of vitamin D from different sources is another method of assay which Upjohn research workers helped to develop and perfect. Leghorn chicks in groups of ten were fed basal diets with vitamin D supplements from such sources as cod liver oil, tuna liver oil, albacore liver oil. Bone ash determinations upon the pooled left tibiae of each group indicated the efficacy of vitamin D from these sources.

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(ethinyl estradiol)

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Specificity is reflected in speedy relief, often within as few as three days;[1] in marked improvement in general well-being;[2] in the virtual "absence of side reactions if minimal effective doses are administered"[3]; and in economy—less than five cents per day.

ESTINYL Tablets are available in 0.05 and 0.02 mg. strengths. Bottles of 100, 250 and 1000 tablets. Also available in 0.5 mg. strength. Bottles of 30 and 100 tablets. ESTINYL Liquid containing 0.03 mg. per 4 cc. Bottles of 4 and 16 oz.

(1) Lyon, R. A.: Am. J. Obst. & Gynec. *47*: 532, 1944. (2) Cooper, M. J., and Bishkind, G. R.: J. Clin. Endocrinol. *3*:703, 1942. (3) Wiesbader, H., and Filler, W.: Am. J. Obst. & Gynec. *51*:75, 1946.

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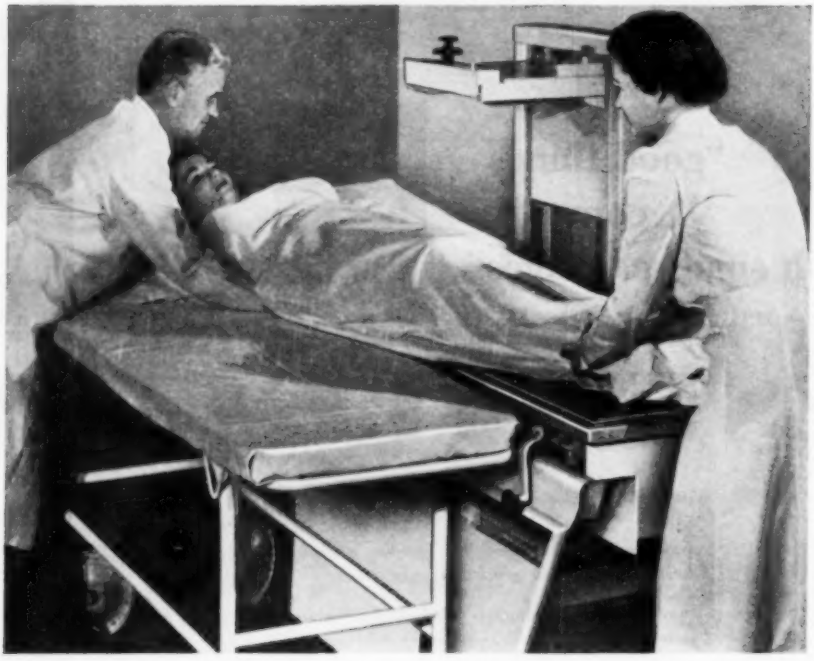
It's NEW!



More than just a new x-ray unit, the Maxicon is a fundamentally new idea for a comprehensive line of x-ray apparatus. Specifically designed to grow with your practice, the Maxicon permits you to choose only the x-ray facilities you actually want or require. Comprised of a number of components that can be assembled in various combinations, it covers the range of diagnostic x-ray apparatus from the horizontal table to the motor-driven combination unit.

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8. Motor-Driven Fluoroscopic Unit. Operator's hands are free, for palpation of patient and manipulation of controls. Scattered-radiation protection and automatic field-limiting device are important.

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F. Netter M.D.

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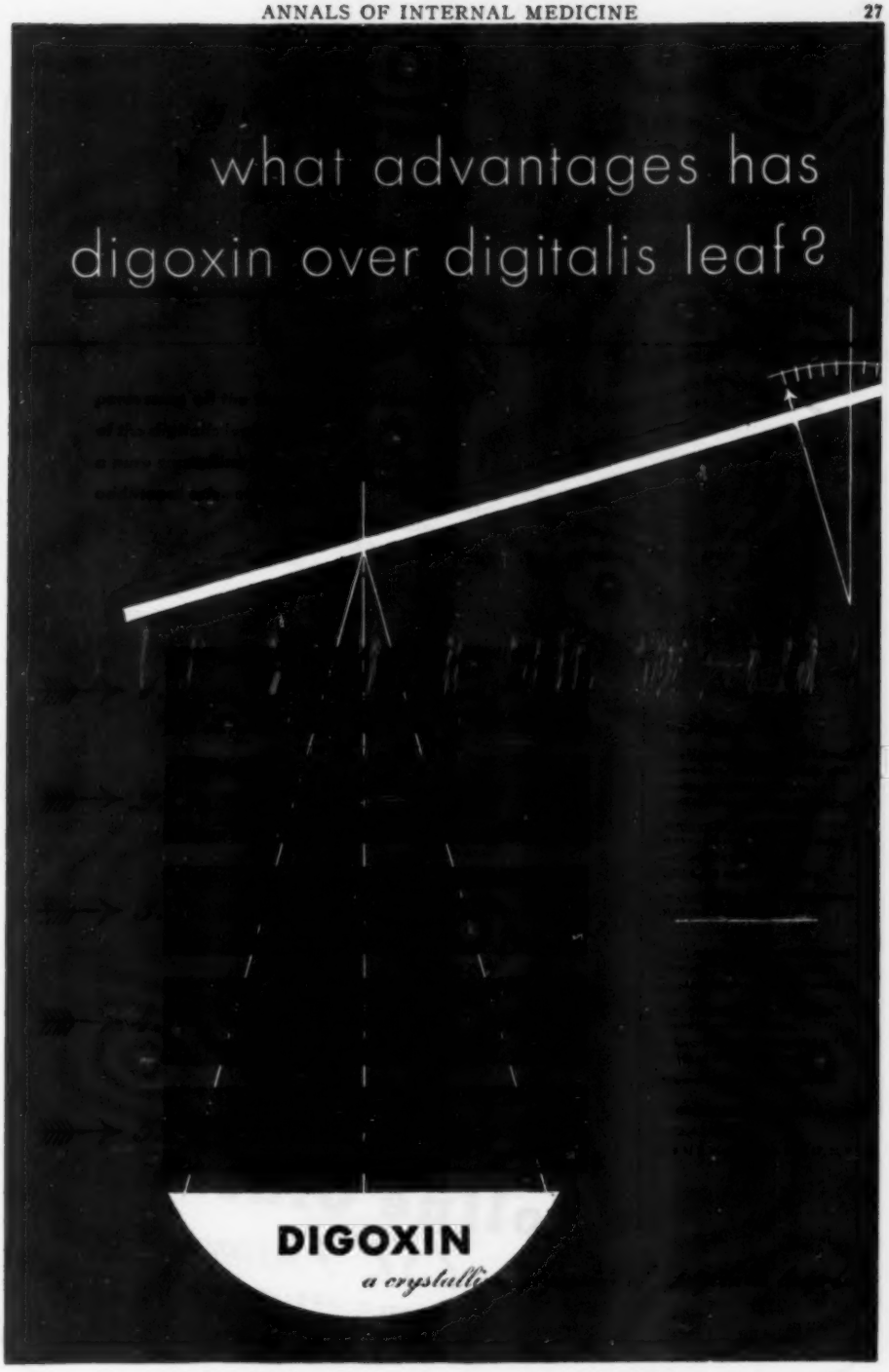
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Containing 61.7% choline gluconate or the equivalent of 25% choline base, Solution Choline Gluconate-C.S.C. provides an exceptionally large amount of choline base equivalent per teaspoonful. *Adequate* dosage may be given for utmost therapeutic value. This greater choline content is made possible by the high concentration of the choline gluconate salt.

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SUPPLIED: Bottles of 100, 500, and 1,000.
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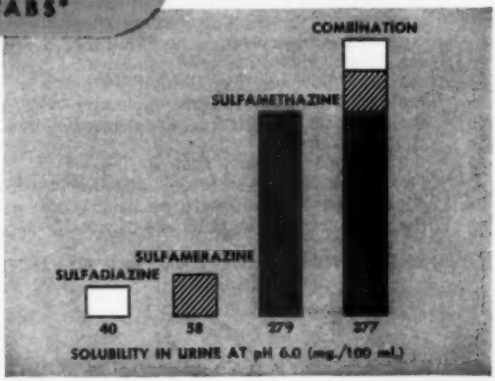

1. Flippin, H. F., and Boger, W. P.: Virginia M. Monthly 76: 56 (1949).
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The sound and wholesome nutritious diet is an integral part of modern day preventive and definitive therapy. A steady stream of adequate amounts of all the essential nutritional elements is vital for good growth, maintenance of tissue structure and functioning, healing after trauma, and resistance to infection. For maintaining this daily, steady stream of nutrients, however, conditions both in health and illness often make imperative the use of an efficient food supplement along with the diet.

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Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	676	VITAMIN A	3000 I.U.
PROTEIN	32 Gm.	VITAMIN B_1	1.16 mg.
FAT	32 Gm.	RIBOFLAVIN	2.0 mg.
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Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

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salt without sodium

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Neocurtasal, completely sodium free salt, palatably seasons all foods. Neocurtasal looks and is used like ordinary table salt.

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Available in convenient 2 oz. shakers and 8 oz. bottles.

Write for pads of diet sheets.

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"The results were uniformly good... None of the patients exhibited any evidences of intolerance to Dienestrol, nor was there a single instance of postnatal hemorrhage."[1]

For suppression of lactation as well as management of other conditions in which estrogen therapy is indicated, accumulated evidence shows White's Dienestrol to be a "potent, safe, and unusually well-tolerated"[2,3] estrogenic substance.

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White's DIENESTROL

ACCEPTED Council on Pharmacy and Chemistry American Medical Association

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SUSPENSION	In 10 cc. multiple dose, rubber-stoppered vials. When vial is thoroughly shaken each cc. contains 5.0 mg. of Dienestrol.

WHITE LABORATORIES, INC., *Pharmaceutical Manufacturers*, Newark 7, N. J.

1. Rakoff, A. E., Paschkis, K. E. and Cantarow, A.: J. Clin. Endocrinol. 7:688 (Oct.) 1947.
2. Finkler, R. S., and Becker, S.: Am. J. Obst. & Gynec. 53:513 (Mar.) 1947.
3. Finkler, R. S., and Becker, S.: J. A. M. W. A. 1:152 (Aug.) 1946.
4. Sevringhaus, E. L.: J. Omaha Mid-West Clin. Soc. 8:28, 1947.
5. Sikkema, S. H., and Sevringhaus, E. L.: Am. J. Med. 2:251, 1947.

Choline
(Flint)

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what it is...

Choline is a component of the lecithin molecule, and is the most important known *Lipotropic Agent*. The term "lipotropic" describes the action of those dietary substances which help prevent or remove excessive fatty deposits in the liver.

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Supplementary choline therapy is being employed in the dietary management of hepatic insufficiency; in early and late cirrhosis; in the treatment of chronic or threatened liver involvement associated with diabetes, malnutrition, poisoning by hepatoxic agents and in various infectious processes.

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palatable "Syrup Choline *(Flint)*"

—25 per cent W/V—containing one gram of choline dihydrogen citrate in each 4 cc.—supplied in pint and gallon bottles.

"Choline Capsules *(Flint)*"

—containing 0.5 gram of choline dihydrogen citrate per capsule—are supplied in bottles of 100, 500 and 1000.

For your copy of "The Present Status of Choline Therapy in Liver Dysfunction," write—

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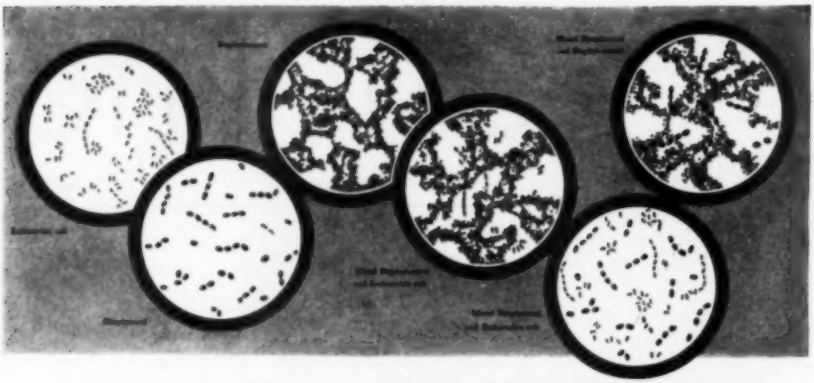

a wide antibacterial range in urinary-tract infections

Extensive clinical use[1,2,3,4] has established the dependable effectiveness of MANDELAMINE* against organisms commonly found in urinary-tract infections. This fact simplifies treatment, as the administration of MANDELAMINE can be started without awaiting laboratory reports on the organisms involved.

MANDELAMINE is exceptionally well tolerated. Its use is not attended by the danger of crystalluria, and gastric upset or other distressing side-effects are rarely observed. Bacteria seldom, if ever, develop resistance to this drug as they sometimes do to other chemotherapeutic agents and antibiotics. Dietary or fluid regulation is not required. No supplementary acidification is necessary except where urea-splitting organisms occur.

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MANDELAMINE is supplied in bottles of 120, 500, and 1,000 enteric-coated tablets. It is available through all prescription pharmacies.

Complete literature and samples to physicians on request.

1. Butt, A. J.: J. Florida M. A. 35: 430 (1949). 2. Carroll, G., and Allen, H. N.: J. Urol. 55: 674 (1946). 3. Kirwin, T. J., and Bridges, J. P.: Am. J. Surg. 52: 477 (1941). 4. Scudi, J. V., and Duca, C. J.: J. Urol. 61: 459 (1949).

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BRAND OF METHENAMINE MANDELATE

Iron in adequate dosage

"is almost a physiological necessity in infancy and childhood and [childbearing] women . . ."

Sundaram, S. K.: Lancet. 1:568, 1948

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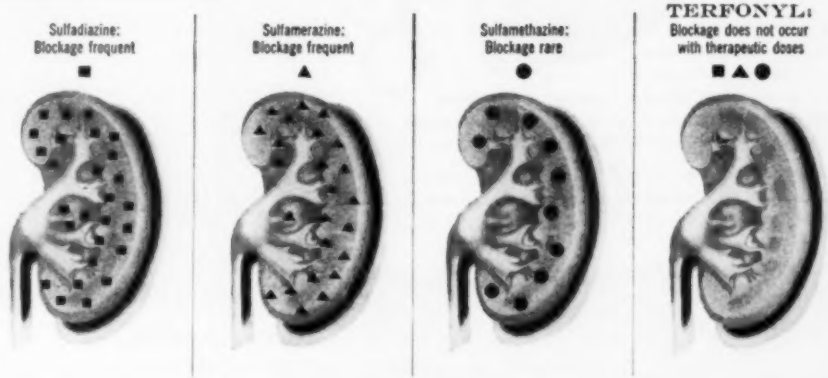

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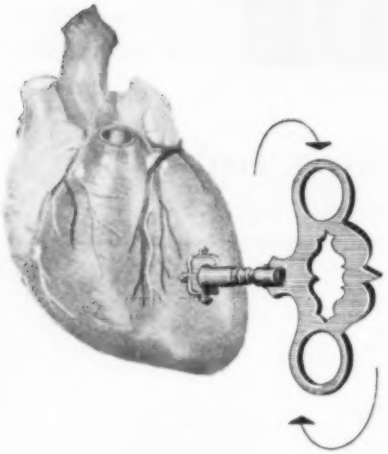

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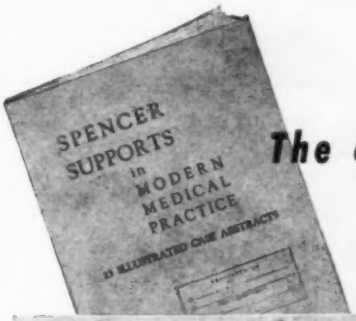

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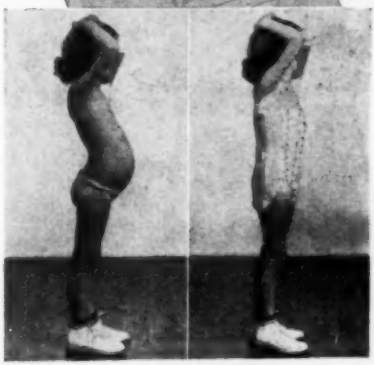

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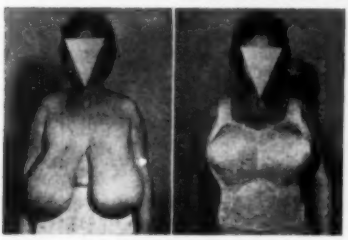

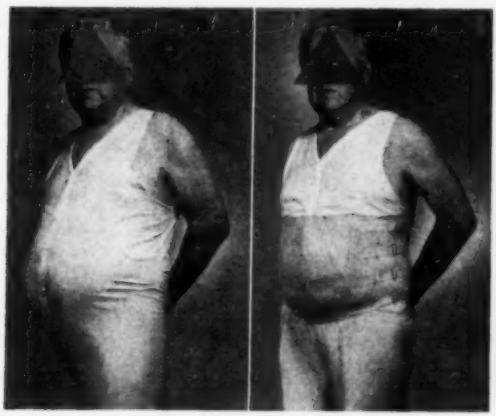

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ANNALS OF
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THE ACUTE RADIATION SYNDROME IN MAN *

By SHIELDS WARREN, M.D.,† and JOHN Z. BOWERS, M.D.,‡
Washington, D. C.

IONIZING radiation today embraces a variety of atomic particles and electromagnetic waves some of which penetrate the body at will while others, although highly damaging, are effective only over a range of a few millimeters of tissue. When an atomic bomb explodes, two forms of penetrating radiation, namely gamma rays and neutrons, are instantaneously liberated in large amounts. The passage of these radiations through the body of an individual will, if in sufficient amount, damage a variety of tissues according to their inherent "sensitivity" to radiation. This injury to sensitive tissues produces a collection of signs and symptoms which are sufficiently unique and recognizable to deserve the title, "acute radiation syndrome." Actually, this syndrome is not restricted to ionizing radiation from external sources. The assimilation in sufficient quantity of radioactive elements which distribute themselves throughout the body may produce a similar picture—this has not occurred in man.

There are many interesting and more or less unsolved aspects of the effect of radiation on living systems. The remarkable variation in the sensitivity of the tissues of the body to ionizing radiation is pertinent. Table 1 lists the tissues of the body in order of decreasing sensitivity.[1, 2] Perusal

TABLE I

Radiation Sensitivity of Tissue

a. Lymphocytes	*h.* Connective tissue
b. Erythroblasts	*i.* Bone
c. Germinal epithelium of testis	*j.* Liver
d. Myeloblasts	*k.* Pancreas
e. Epithelium of intestinal crypts	*l.* Kidney
f. Germinal cells of ovary	*m.* Nerve
g. Basal layer of the skin	*n.* Brain
o. Muscle	

* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

† Director, Division of Biology and Medicine, U. S. Atomic Energy Commission.
‡ Deputy Director, Division of Biology and Medicine, U. S. Atomic Energy Commission.

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of this list reveals that, in general, those tissues which are most sensitive are those which are characterized by the shortest life span and the most rapid metabolic processes such as the synthesis and degradation of ribose- and desoxyribose nucleic acid. All cells vary in their sensitivity to radiation according to the phase of mitotic activity and the cell in early prophase is the most sensitive to injury by radiation.[3]

It is important to realize that the syndrome here discussed is produced by near-total or total body exposure to excessive amounts of radiation—it is not produced by localized exposure. For example, one-fourth of the amount of radiation ordinarily administered therapeutically to a carcinoma of the cervix will, if given over the total or near-total body, prove fatal to one-half of the individuals so exposed.

Of more scientific than practical interest here is the remarkable variation which occurs between species in their sensitivity to radiation. Thus, the guinea pig will succumb to one-half of the amount of radiation required to produce a similar effect in man, while man will succumb to approximately one-half of the amount of radiation required to produce a similar effect in the rabbit. Table 2 lists the various sensitivities of man and the more common laboratory animals.[4, 5]

TABLE II

Guinea pig	175r to 250r
Dog	325r
Goat	350r
Mice	530r
Rats	600r
Rabbits	800r
Man	between goat and mouse—circa 450r

Although most bacteria show little evidence of harm with a dose of 100,000 roentgens, half of the eggs of the fruit fly, Drosophila, are killed by 155 roentgens.

Again, there is a variation in sensitivity within species as exemplified by the variation in hematologic response to an injurious dose of radiation accidentally received by three cyclotron workers. While one man showed a pronounced fall in the white blood count, another showed only a mild reaction, while the third showed no change.

The largest volume of data on man results from the work of the Japanese investigators and the members of the Joint Commission which worked in Japan in the Fall and Winter of 1945 for the Medical Departments of the Army and the Navy and the Manhattan Engineering District to accumulate knowledge from study of those individuals exposed to the atomic bomb explosions at Hiroshima and Nagasaki.[6, 7, 8, 9, 10] From this group there are approximate data on several thousand survivors, detailed data on several hundred and autopsy material which is not too abundant, but nevertheless informative, on those dying from a few days after the bombing to some months later. Approximately 100,000 survivors at Hiroshima and Nagasaki received from just sublethal to infinitesimal doses of ionizing radiation.

Of these, a great majority are well, aside from the deformities referable to burns and other injuries. The study of the survivors is now being carried on by the Atomic Energy Commission through the Committee on Atomic Casualties and the Atomic Bomb Casualty Commission of the National Research Council.

Pathogenesis

There has been considerable research activity in regard to the mechanism of the effects of radiation on the body, and the laboratories of the Atomic Energy Commission are studying this problem intensively. Failla [11] and Sugiura [12, 13] have proposed that the degree of hydration of cells is closely related to their sensitivity to radiation, the edematous cell being most sensitive. Others [14, 15] have considered that the production of ion pairs within the sensitive structure produces the characteristic changes—the target theory. The succession of events which occurs when ionizing radiation penetrates a tissue are in order—physical, chemical and biological.[16] Thus, there is first a physical absorption of the ionizing radiation by the molecules which constitute the human body. There then follows a series of chemical changes which are not understood in detail. Barron [17] however, has shown that those enzymes which contain sulfhydryl groups are easily inactivated by ionizing radiation and that they may be reactivated by the introduction of reducing agents which contain sulfhydryl groups. Support for this concept is evoked from the fact that the passage of ionizing radiation through water causes ionization with subsequent dissociation into a hydrogen ion and a hydroxyl radical. In the presence of molecular oxygen there may then occur the formation of hydrogen peroxide, and some of the injurious effects of ionizing radiation have been attributed to this reaction. The fact that cysteine and glutathione have been shown to exert a protective effect in animals tends to support this theory.[18]

Finally, there are those pathological effects resulting from these successive physical and chemical reactions which can be detected microscopically in the tissues of the body. It is to the more sensitive tissues of the body that we look for pathologic change and from these changes we attempt to explain the clinical manifestations that ensue.

Histopathology

The histopathological effects of radiation include changes in the cells, in the stroma and in the blood vessels. The *cellular* effects include cessation of mitosis which occurs promptly, followed by disorganization of the structure of the cell and swelling of the cell. As the cell resumes mitosis, bizarre mitotic figures appear. The *stromal* effects are first manifest as swelling which is followed frequently by fibrosis and hyalinization. The initial *vascular* effects are thrombosis which may, in turn, be followed by fibrosis, hyalinization and telangiectasia.

Liebow, Warren and DeCoursey [19] have recently summarized the pathological studies of the Japanese casualties. The bone marrow in these cases showed in the early period a complete disappearance of all blood-forming elements except scattered areas of erythropoiesis. At the beginning of the second week the proliferating reticulum had differentiated sufficiently to form lymphocytes and plasma cells, and in the fourth week myeloid differentiation was apparent. Later, the marrow showed hyperplasia with maturation arrest which finally disappeared.

The lymphoid tissue showed a disappearance of lymphocytes by the third day with resultant decrease in the size of the node. The lymphocytes returned slowly and at three months were still reduced in number.

As early as the fourth day the testes showed extensive necrosis of the germ cells with subsequent hyalinization. The Leydig cells became prominent, apparently a true hypertrophy.

The ovaries showed less striking changes characterized by an absence of corpora lutea.

The gastrointestinal tract showed early and pronounced changes with mucosal edema extending into the submucosa with pseudo-membrane formation associated with extensive ulcerative change. The muscularis and serosa were free from specific radiation change.

Symptomatology

The diverse effects of irradiation upon the body produce a variety of clinical signs and symptoms which can in many instances be explained by the observed pathology. In other instances, it appears that a physiological basis, as yet undemonstrated, should be invoked. In all instances, the symptoms, their severity and their time of appearance are conditioned by the severity of the injury and the sensitivity of the individual.[20, 21, 22]

Asthenia: In the premonitory stages of the acute irradiation syndrome there is usually pronounced weakness which is without adequate explanation. Subsequently, the degree of prostration is in proportion to the related signs and symptoms, especially those of diarrhea and anemia.

Diarrhea: The sensitivity of the gastrointestinal mucosa to irradiation and the significance of this in clinical medicine have been emphasized by Warren, Whipple and others.[23, 24] In individuals who have received damaging doses of total body irradiation, transient diarrhea appears during the premonitory stage and subsides rapidly. With the onset of the full-blown clinical picture, diarrhea is increasingly severe and, no doubt, contributes greatly to the fatal outcome in many of the cases through the intensive loss of salt and water that occurs through the bowel. In addition, the debrided gastrointestinal mucosa may serve as an easy avenue of entry for organisms which subsequently appear in the blood stream. In those Japanese most severely injured, diarrhea appeared the day after the bombing; the stools were at first liquid but frequently as the syndrome progressed they became blood streaked or grossly bloody.

Nausea and Vomiting: During the premonitory phase these symptoms are pronounced and may reappear subsequently with considerable severity.

Petechiae and Purpurae: Among the hematologic manifestations of the disease none has received more attention than these.[25, 26, 27] Total body irradiation causes a rapid and pronounced fall in the blood platelets, damage to the blood vessel walls and, in at least some animals, the appearance of a circulating anti-coagulant resembling heparin. The earliest change is increased capillary fragility, followed by thrombopenia with subsequently the appearance of the anti-coagulants. Purpurae and petechiae appear from four to seven days after the initial injury and may be associated with bleeding from the body orifices. These manifestations reach their peak between the sixteenth and twenty-second day.

Mucosal Ulcerations: Severe ulcerative lesions of the mucous membranes appear at the end of the second week. These necrotic lesions may be quite extensive with pronounced secondary infection. Laryngitis, tonsillitis and pharyngitis may all be a part of the picture, and ulceration of the female genitalia has been noted as well as small superficial ulcerations of the skin.

Epilation: One of the most interesting manifestations of the acute irradiation syndrome is the localized, extensive loss of hair from the scalp.[28] In most cases, such epilation has appeared about two weeks after exposure and has shown no sexual predilections. In many instances, the pattern was the same as that for baldness in the male but in some severely irradiated cases it was complete. The hair regrew in all individuals that survived and ultimately had the same texture and color as the original. The hair of the chin, axillae and pubic area showed alterations in only a small percentage of the cases.

Fever: In the fulminating cases, fever appeared the day after the bombing while in others that were less severely injured an interval of seven to 10 days supervened before the onset of fever which often showed a step-like rise until death.

Tachycardia: The pulse rate is frequently accelerated out of proportion to the other visible evidences of injury.

Clinical Course

The acute radiation syndrome may take several forms according to the severity of the exposure.

The *fulminating* form is characterized by the onset of nausea, vomiting, prostration and mild diarrhea within two to six hours after exposure. These manifestations gradually increase in severity and are associated with a pronounced fall in the white blood count. The diarrhea becomes severe and grossly bloody stools may appear. There is a step-like rise in fever *and* death occurs from the fifth to the tenth day. This occurs in individuals who have received amounts of irradiation far greater than recognized lethal levels.

The *hemorrhagic* form of the disease presents initially nausea, vomiting, prostration and, at times, mild diarrhea of about two days' duration. A well period of about five days then ensues only to be followed by profound prostration, bloody diarrhea and increasing fever. Petechiae and purpurae appear and are associated with frank bleeding from body orifices. Ulcerative lesions of mucosal surfaces become increasingly extensive and death may occur from three to six weeks after exposure. Patients in this group have received irradiation doses in the lethal or near lethal range.

A number of the patients in the hemorrhagic group will survive the three to six weeks period but exhibit continued weakness, pallor and ulcerative lesions characteristic of the *pancytopenic* form of the disease. Finally, cachexia may become pronounced and death ensue after a prolonged period of illness.

Laboratory Findings

The *hematologic* responses are of the greatest interest. Following exposure there may occur a neutrophilic leukocytosis persisting for 24 hours; in some cases with extremely high exposures this may not occur. It is felt that this does not represent a direct effect of irradiation but rather a mobilization of the white blood cells. At both Hiroshima and Nagasaki, patients who were examined the first few days after the bombings showed a leukopenia which was most pronounced in the lymphoid series and subsequently in the myeloid elements. The platelet count fell less rapidly than the white blood count and was followed by a fall in the red blood cell count. Reticulocytes uniformly disappeared from the peripheral blood within a short time. In the cases surviving for six weeks, the anemia often became quite pronounced and reached levels as low as 800,000 to 900,000 RBC cu. mm.[7, 8, 9]

The pattern of change in the blood picture varied according to the dose received. In the most severely injured cases the white blood count usually reached levels less than 1500 per cu. mm. According to Leroy[9] recovery was rare in patients whose count dropped below 600. Examination of the blood films revealed predominantly lymphocytes and the anemia continued to increase for a period of time after the white blood count had reached its minimum level. This finding is of importance in planning transfusion therapy. In the less severely injured cases anemia often becomes the most pronounced finding.

Seminal Fluid: Liebow et al.[10] examined a group of Japanese men 10 weeks after the explosions and found instances of pronounced hypospermia or azospermia. In many individuals who survived, the sperm count returned to normal over a period of from six months onward.

There is little information on other laboratory studies which might have been done on the Japanese. From studies in animals we know that there will be a marked prolongation of the sedimentation rate.

Complications

In the Japanese, the picture of the acute irradiation syndrome was distorted by the pronounced and often fatal traumatic and thermal injuries. Indeed, in many instances, the patients died from these injuries before the clinical and pathological pictures of acute irradiation injury had developed.

Bacterial infections of a local or generalized nature may be prominent. Phagedenic ulcers were seen in the Japanese and although there were no facilities for bacteriological study in the fatal cases, the histopathological studies revealed clumps of gram negative and gram positive organisms in many of the tissues. Undoubtedly, bacterial invasion of the blood stream could be easily accomplished through the damaged gastrointestinal mucosa or through the numerous mucosal and epithelial ulcers which occur throughout the body. In addition, the lungs in many instances showed areas of so-called "neutropenic" pneumonitis.

A number of the Japanese who exhibited the subacute type of illness developed lung abscesses, others developed miliary tuberculosis.

Sequelae

Observations on animals as well as a consideration of what human data have been accumulated on accidental chronic exposures to irradiation suggest that several late sequelae might develop. At this time, extensive studies are in progress in Japan with a view to detecting the development of these, but as yet there are no positive results.

Experience with animals suggests the desirability of searching for evidence of genetic changes in the survivors. Effects on the germ plasm may be evident as a mutation or a chromosome break in which there is an alteration of the position of the genes within the chromosomes. These changes when induced by radiation are usually lethal to the embryo. If survival occurs they are recessive in character.

The possibility of late neoplasia is suggested by the fact that there has been an increased incidence of neoplasms in animals exposed to irradiation and humans have developed bone sarcomas [29] following irradiation therapy of bone tumors or overlying soft tissue tumors. The high incidence of leukemia in radiologists and laboratory studies in animals suggest the necessity of careful observation for signs of this disease.[80]

The profound changes which occur in the bone marrow indicate that the possible subsequent appearance of blood dyscrasias other than leukemia should be kept in mind.

Therapy

The treatment of individuals exposed to damaging amounts of ionizing radiation is at this date supportive and non-specific, i.e., there is no known specific agent which will, post-exposure, ameliorate the injury. It is known

from observations on large animals intentionally exposed at Bikini that liberal and repeated transfusions of fresh blood are useful. Folic acid, liver extract, pyridoxine and pentnucleotide have been administered to irradiated laboratory animals in liberal amount with questionable benefit. Allen et al.[25] have administered to irradiated dogs anti-heparin substances, such as protamine and toluidine blue, with a significant reduction in mortality. Field and Rekers [31] have reported that rutin will produce a significant reduction in the mortality rate of irradiated dogs. There has been no opportunity adequately to evaluate these measures in man.

The rapid development of dehydration in the exposed Japanese, accounted for in part by the large amounts of salt and water lost by bowel, suggests the importance of close attention to aberrations in blood electrolytes and the institution of parenteral therapy for their correction. This aspect of radiation injury is deserving of considerable study. In this regard it should be recognized that with the extensive damage of the gastrointestinal mucosa that ensues, there will be a sharp reduction in absorption of nutrients and parenteral alimentation will be indicated.

The Japanese fatalities showed, in many instances, bacteremia and/or septicemia which, it is felt, was in a measure due to invasion of pathogens from the gastrointestinal tract, as well as by other avenues, aided and abetted by the concomitant agranulocytosis. Preliminary observations suggest that the administration of antibiotics to combat infection by gram negative and gram positive organisms would assist in lowering the mortality from these causes.

The question naturally arises as to the value of the numerous agents which have been tested, some with reported success, in the therapy of radiation sickness which follows x-ray therapy. Adrenal cortical hormones, both desoxy-corticosterone and the whole extract, have been reported by Ellinger [32] to alleviate promptly nausea, vomiting and prostration in patients. Other investigators have studied the effect of these materials on laboratory animals after lethal and near lethal exposures and found no significant lowering of mortality.[33] Further study is indicated; the salt retaining properties of the adrenal cortical hormone might prove helpful.

It has been noted in the beginning of this paper that several agents have been shown to lower the mortality if administered before exposure to irradiation. Unfortunately, none has been shown to affect mortality rates after exposure.

The statistics from Hiroshima and Nagasaki showed that approximately 60 per cent of the deaths were due to trauma, 30 per cent to burns and only 10 to 20 per cent to irradiation. It should be apparent that in many instances individuals succumbed to trauma or burns before the ionizing radiation syndrome had developed and that, in all probability, many more would have died from irradiation had they been salvaged from the effects of trauma or burns.

Prognosis

The patients who develop the *fulminating* course have undoubtedly received amounts of radiation far in excess of the minimum lethal dose. However, in those exhibiting the *hemorrhagic* and the *pancytopenic* forms of the disease, one is at or beneath the lethal range and, accordingly, it should be anticipated that a number of patients in this group could with proper care be salvaged.

Since the patients in the hemorrhagic and pancytopenic groups also exhibit a well period between the premonitory phase and the development of the full blown clinical picture, this occurrence should be looked on as a favorable sign.

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EVALUATION OF HISTAMINE AND CHOLINESTERASE IN ALLERGIC PHENOMENA *

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The current consensus leans to the view that serological reactions play an important, if not essential, rôle in initiating allergic events, and that the subsequent elaboration of histamine or a histamine-like substance, completes them. Some believe the above is not the whole story, and that other factors contribute to complete the allergic phenomenon, i.e., the possible part played by the vegetative nervous system and by altered tissue states. Many theoretical and factual observations have been made during the past generation in support of these views. Many facets of the picture have been explored, but others remain for consideration or elaboration.

The present communication will confine itself to a consideration of some factors other than the serological. If one could conceive of a completely healthy animal, it must be assumed that in such there is a perfect balance between all forces which play a part in its attainment. Cannon [1] has coined the word "homeostasis" to denote a tendency to stability in normal body states. Ordinarily, uniformity in vital processes is due to elaborate opposing controls. The vegetative nervous system and its specific chemicals provide one means by which homeostasis may be maintained. The adrenergic (sympathetic) and cholinergic (parasympathetic) divisions oppose each other physiologically.

Excessive or subnormal tonus of one or the other division of the vegetative nervous system would upset homeostasis. The following schematic presentation will show at a glance that when there is a perfect balance between the nervous elements homeostasis prevails. It also indicates factors which sometimes affect balance (enzymes, detoxification, etc.). The many variants in physiological reactions following upsets in the balances provided could be discussed at length but all possibilities are deducible from this scheme save those introduced by histamine. This scheme does not include the effects of acetylcholine on the sympathetic ganglia since it is questionable whether enough of this chemical escapes into the general circulation to affect them. There is also some evidence that histamine may sometimes act through the agency of the cholinergic nervous system.[2]

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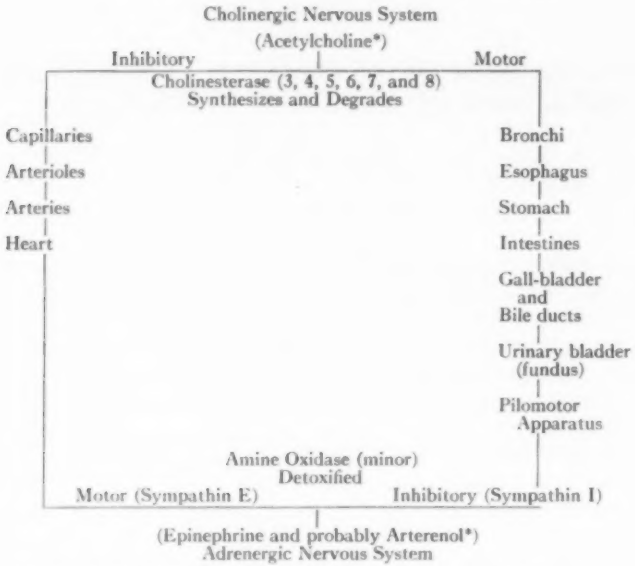

* Specific chemicals elaborated by the two divisions of the vegetative nervous system.

Experimental

I. Possible Rôle of Cholinesterase in Allergy. Much has been written about cholinesterase activity in health and disease.[3, 8] Our results with an extensive examination of cell and serum cholinesterase in health and disease concur largely with these. We also studied their relationship to blood specific gravity and found no parallelism. In regard to allergy, there have also been prior observations indicating normal cholinesterase activity. However, we felt that this disease warranted further consideration with respect to cholinesterase activity.

The values for cell and serum cholinesterase herein reported were obtained by the methods outlined by Alles and Hawes.[6] Blood specific gravity figures were according to the procedure of Barbour and Hamilton.[9] Blood serum proteins were determined as recommended by Howe [10] and blood chlorides were estimated in the way devised by Schales and Schales.[11]

The results tabulated in table 1 show cell cholinesterase values arranged in ascending order. Total and serum cholinesterase values are not always parallel. Likewise, there appears to be no uniform relationship between cholinesterase values and other blood constituents and properties. Low values, when found, are probably more the result of concurrent disease than allergy per se.

Experience of others, as well as that of ourselves, indicates that blood

TABLE I

Cholinesterase and Other Factors in Allergic Individuals

Color	Sex	Age	Diagnosis	Activity	Cell Cholinesterase	Total Cholinesterase	Serum Cholinesterase	RBC	HGB Grams %	Hematocrit	Specific Gravity	Serum Protein	Chlorides	Temp.	Pulse
W	M	46	Bronchial asthma, chronic glomerulonephritis, pneumonia?	++	0.195		0.692		10.5	31	1.0459	5.6	550	99.0	104
B	M	18	Asthma, severe	+	0.205	0.635		5.9	16.2		1.0629	7.8		98.6	86
W	F	54	Derm. venenata, derm. medicamentosa	+	0.205	0.585		4.3	14.0			6.5	480	97.6	76
W	F	65	Derm. medicamentosa	+	0.215		0.535	4.8	11.7	38	1.0477	5.9		100.6	82
W	F	25	Hay fever	+−	0.235	0.570		5.1	14.5			6.9			
B	M	18	Asthma	−+	0.250	0.580		5.2	14.8			7.3		98.2	84
W	F	25	Hay fever	+	0.255	0.605		5.2	13.8			6.6			
W	F	15	Urticaria, bulbar polio	+	0.265	0.625		4.1	11.9			6.0		99.8	82
W	F	49	Asthma, hay fever	−	0.270		0.695		13.4	43	1.0533	7.2			
W	M	69	Derm. venenata	+	0.280	0.595		4.5	14.0			7.3		98.0	80
W	M	46	Bronchial asthma, chronic glomerulonephritis, poss. periarteritis nodosa	+	0.288		1.365		10.8	34			550	98.2	80
W	F	47	Hay fever	−	0.290	0.760		4.5	13.8			.67			
W	M	69	Derm. venenata	+	0.295	0.395		3.8	13.0				450	97.0	69
W	M	69	Derm. venenata	+	0.300	0.615		5.3	13.5				500	97.2	60
W	M	32	Hay fever, chronic rhinitis	+−	0.312		0.865		14.0	45	1.0523	7.2			
W	F	24	Allergic rhinitis	−	0.315		0.525		11.9	37	1.0484	6.5			
W	F	34	Urticaria	+	0.315	0.620		5.3	14.3		1.0570	6.6		98.8	68
B	F	32	Allergic rhinitis	−	0.317		1.060		13.2	44					
W	M	40	Actinomycosis of kidney; perirenal abscess; blood drawn after disappearance of urticaria	−	0.330	0.815	0.715		12.6	42	1.0536	8.7	485	98.0	84

TABLE 1—*Continued*

Color	Sex	Age	Diagnosis	Activity	Cell Cholinesterase	Total Cholinesterase	Serum Cholinesterase	RBC	HGB Grams %	Hematocrit	Specific Gravity	Serum Protein	Chlorides	Temp.	Pulse
W	F	40	Allergic rhinitis	−	0.340		1.020		13.2	42	1.0510	7.0			
W	M	54	Headaches, sneezing	−	0.355		1.000		14.7	47	1.0555	7.0			
W	M	40	Urticaria	+	0.355	0.640		5.0	12.2		1.0559	8.5	485	98.0	96
W	F	20	Sneezing, rhinorrhea	−	0.365		0.757		13.0	42	1.0521	6.7			
W	F	15	Post polio, post urticarial	−	0.375	0.885		4.1	13.4		1.0562	7.2		99.8	82
W	F	62	Hay fever	−	0.380		0.925		13.4	42	1.0526	7.2			
W	M	31	Thrombo-angiitis obliterans, urticaria	+	0.435	0.840		6.6	15.8		1.0580	6.4	460	98.6	96
W	M	55	Bronchial asthma, poss. periarteritis nodosa	+	0.435		0.890			45	1.0547	6.5		97.4	92
W	M	27	Urticaria, aneurysm, RHD, subacute bact. endocarditis	+	0.457		1.377	4.9	14.3	46	1.0543	7.8		98.4	88
B	M	61	Silicosis, asthma, duodenal ulcer, neurofibromatibial nerve	−	0.485		0.885		14.0	48	1.0547	7.2		98.6	88
W	M	42	Food and dust allergy, dil. of heart, fibrosis of lung following tbc. bronchiectasis	−	0.495							6.4		98.2	88
W	M	28	Asthma	−	0.505		0.980		16.3	52	1.0592	7.5			
W	M	55	Bronchial asthma, poss. periarteritis nodosa	+	0.507		0.760		15.2		1.0541	6.3		98.8	80
W	F	33	Bronchial asthma	+			1.037	4.9	12.5		1.0578	7.4	460	99.6	100

RBC—red cell count.
HGB—hemoglobin.
Specific gravity—specific gravity of whole blood.
+ = active.
− = inactive.
+− = slightly active.
−+ = very slightly active.

cholinesterase normally varies, quantitatively, over a rather wide range both inter- and intra-individually. The normal range is between 0.7 and 1.25 ml. per 20 minutes. In those critically ill with liver disease, tuberculosis, and rheumatic fever, the values tend to be low. In contemplating the possible part played by cholinesterase activity in allergic phenomena, it must be realized that all observations have so far been made only on venous blood. Changes in their activities locally have not been investigated, probably due to inherent difficulties of experiment. The part played by the cholinergic nervous system in allergic phenomena cannot be ruled out by the finding of normal cholinesterase values since it is entirely possible that in these conditions there is hypersensitivity to acetylcholine. Such has been found to be the case with histamine as described later.

II. Possible Part Played by Histamine in Allergy. Just where histamine fits into the picture of homeostasis is hard to imagine. It is more likely to upset equilibrium in vital phenomena than to help balance. Histamine is probably formed by decarboxylation of histidine. Dale and Laidlaw [12] first noted its occurrence in biological material, namely in ergot. They also demonstrated its tonic effect upon unstriated muscle. Lewis [13] ascribed local skin reactions to mechanical stimuli to an H-substance, histamine, or a histamine-like material. Best and McHenry [14] determined the quantity of histamine in various tissues by way of acid hydrolysis. Barsoum and Gaddum modified this procedure.[15] Code [16] further improved the method and ascertained its range of accuracy. Best and McHenry [17] summarized the work on histamine to 1931, as did Dragstedt and Mead [18] to 1937. Rose and Browne [19] and Rose [20] investigated histamine relationships to experimental shock and to certain allergic states, using the Code procedure. The values reported before and after inducing allergic reactions were far from consistent, high values appearing during symptoms in only one or two instances of 15 cases. Katz and Cohen [21] also used the Code method to demonstrate the liberation of histamine by whole human blood when specific allergens were added, with incubation for 15 minutes at 37° C. Their results are quite consistent. Rosenthal and Tabor [22] have now demonstrated the utility of an old colorimetric method in conjunction with McIntire, Roth, and Shaw's [23] cotton acid succinate isolation procedure in distinguishing between free and bound histamine in animal tissues.

Abel, Rowntree, and Turner [24] demonstrated the usefulness of semipermeable membranes in the isolation of dialyzable substances from the blood. Toth [25] and Rehberg [26] employed viscose tubing in ultrafiltration. We used the Code procedure and simple dialysis of whole blood and serum against Tyrode's solution to distinguish between free and bound histamine.

Experimental

Viscose tubing of 1.46 cm. diameter purchased from the Visking Corporation about eight years ago (the year of manufacture may be important

since its formula may vary) was selected for the work reported below. It was cut into 125 mm. lengths and one end of each piece was plugged, leak proof, with glass. Before using, the viscose was thoroughly washed with distilled water for about 12 hours. The individual lengths contained 10 ml. Tyrode's solution into which dialyses were performed by immersion into 20 by 150 mm. pyrex test tubes having a like quantity of material containing histamine. The optimum time for dialysis was determined to be 120 minutes, when equilibrium was reached. The Code method of recording was then used.

In 10 experiments wherein 0.05 mg. of histamine phosphate was added to 10 ml. of Tyrode's solution, dialyses against like quantities of Tyrode's solution were performed. Fifty per cent of the histamine appeared in the dialysate at all times after 90 minutes up to 960 minutes, the time limit followed. Times less than 90 minutes were inadequate. In 23 of 29 experiments where in each instance the same amount of histamine phosphate was added to 10 ml. portions of pooled human blood serum, at least 72 hours old, 120 minute dialysis against Tyrode's solution yielded 50 per cent recovery in the dialysate. In four experiments the dialysate contained 52 per cent to 55 per cent, and in two cases 48 per cent and 49.5 per cent. In four experiments when the same quantity of histamine was added to 10 ml. portions of pooled human whole blood, 72 hours old and more, and dialyzed against the same volume of Tyrode's solution for 120 minutes there was also at least 50 per cent recovery in the dialysate. It appears, then, that simple dialysis is a satisfactory method for obtaining free histamine quantitatively from human blood. Multiplying the histamine contents of the dialysate by two gives the total amount.

The dialysis procedure was next compared with the method of Code. In 10 experiments with the latter where 0.05 mg. histamine phosphate was added to 10 ml. portions of whole human blood, recoveries of 72 per cent to 110 per cent were obtained, with a mean of 86.3 per cent. Considerable effort was made to obtain more consistent results and better yields by carefully checking each step, but so far this has been unsuccessful. This procedure was employed in duplicate on the same blood specimens and also on aliquots of the filtrates after precipitation with trichloracetic acid. The errors encountered in simple duplicate analyses of fresh human whole blood by the Code procedure were about twice as large as those found in examining the aliquots, in duplicate, of trichloracetic acid blood filtrates. Thus the overall errors must represent losses encountered both in the recovery of histamine in trichloracetic acid filtrates and in their digests with acid. The foregoing means that small differences between histamine contents of blood cannot be demonstrated with certainty by the Code procedure. There is no appreciable or consistent loss of histamine if fresh blood or trichloracetic acid filtrates of fresh blood are preserved in the refrigerator for 24 hours when the Code method is employed. In old pooled blood, simple dialysis yields close to 50 per cent of added histamine in periods of 120 minutes and more.

In fresh blood specimens, the histamine recoveries are uniformly over 50 per cent, no doubt due to varying amounts of histamine already present. Table 2 demonstrates the recoveries of histamine from fresh blood sera both with and without added histamine. The Code procedure reveals the presence of more histamine than does dialysis when further histamine is not added, thus clearly demonstrating that some of it is in a bound form which is physiologically inert when tested on the guinea pig ileum. This table further demonstrates that dialysis yields histamine well over the added amount, probably representing the summation of the free histamine present and that added.

TABLE II

Recovery of Histamine by Dialysis and Code Procedure on Same Blood Specimens

No.	Code	Amount Added	Dialysis
	With Added Histamine		
1.	50.0	100.0	116.6
2.	83.3	100.0	178.0
3.	40.0	50.0	100.0
4.	55.0	50.0	100.0
5.	47.5	50.0	76.0
6.	42.5	50.0	56.0
7.	40.0	50.0	53.3
	Without Added Histamine		
8.	16.3		Present
9.	15.0		Present
10.	66.0		10.0
11.	70.0		10.0
12.	57.5		0

Values are in terms of micrograms of histamine phosphate per 100 ml. of blood. Amounts added are in terms of histamine phosphate.

Employing dialysis and the Code procedure, the dialyzability of bound histamine was demonstrated. The results are tabulated in table 3. Two points were observed. One further revealed that even in the dialysate more histamine was found by the Code method than by direct testing of the dialyzed histamine. Secondly, within experimental error, the same amount of histamine was recovered when the Code procedure was used with whole blood and with its dialysate, thus indicating that all bound histamine is dialyzable and must therefore be in the form of small molecules, most probably the acetyl derivative.

In an effort to determine the source of bound histamine or histamine otherwise formed by acid digestion, the amino acid histidine was added to fresh whole blood in molecularly equivalent amounts to the histamine usually recovered, and treated by the Code procedure with and without 15 minute incubation at 37° C. No increase in histamine over the control values was

TABLE III

Free and Bound Histamine in Dialysates

Two dialysates from same blood specimen. One extracted according to Code and one assayed directly.

No.	Dialysate Plus Code	Dialysate
1.	15.0	5.0
2.	8.8	4.3
3.	35.0	10.0
4.	10.0	5.0
5.	8.8	4.3
6.	9.0	5.0
7.	8.5	4.0

10 ml. blood extracted according to Code and 10 ml. blood from same specimen dialyzed and then treated according to Code.

No.	Code	Dialysate Plus Code
1.	5.0	5.0
2.	15.0	20.0
3.	2.3	2.0
4.	10.0	9.0
5.	5.0	8.5
6.	14.0	20.0

Values are in terms of micrograms of histamine phosphate per 100 ml. blood.

noted. Before final decision on the rôle of histidine in histamine reactions can be made, longer periods of incubation will have to be tried when carefully maintaining sterility.

In table 4 are reported our observations on the blood histamine levels in allergic subjects at different seasons (note dates) and as affected by incubation with specific allergens. It will be seen that blood histamine values as determined by the Code procedure are consistently lower in the summer months than in the winter and that in the patients herein investigated no such high increments in histamine followed incubation with specific allergens as were reported by Katz and Cohen. This was a disappointment since we had hoped to use the method for demonstrating both the source of the histamine and the rôle played by the allergen, i.e., whether or not the allergen was enzymic in action. Future efforts will be directed at establishing the mechanism of histamine formation.

DISCUSSION

The data presented above add somewhat to our understanding of the rôle played by a few physiological factors in the allergic phenomenon. There is need for carrying on investigation of this nature further. Our results with cholinesterase largely concur with those of the other authors. Too much stress should not be placed on blood cholinesterase values as reflecting the non-contribution of the cholinergic nervous system in allergic phenomena. It may well be that allergic subjects are more susceptible to normal amounts of acetylcholine than are normal subjects. Experiments designed to prove this point would be rather heroic in character. That acetylcholine and

histamine may augment the effects of each other is entirely conceivable. Such reactions may occur to increase dilatation of the capillaries and arterioles, promote permeability of the former, and further the spasm of bronchial muscles. Histamine, when injected into normal individuals, is without influence on the bronchial musculature, but bronchoconstriction occurs in subjects with bronchitis, bronchial asthma, emphysema, and cardiac asthma. This was clearly demonstrated by Weiss, Robb, and Ellis.[27] Their experiments demonstrate hypersensitivity to histamine. This may, however, not be direct, but rather, that any smooth muscle stimulant or depressant might be more effective when a delicate trigger mechanism exists.

TABLE IV

Allergic Patients

Allergen added to 10 ml. blood, incubated and extracted according to Code.
10 ml. blood extracted as control

Patients	Date	Allergen	With Allergen	Without Allergen
1	1/26/48	Orris root	60.0	62.0
	2/25/48	Orris root	65.0	—
	7/15/48	Orris root	6.6	7.5
2	2/14/48	Dust	30.0	47.0
	7/12/48	Dust	20.0	16.0
3	1/30/48	Spec. inhal.	75.0	48.0
	3/ 1/48	Spec. inhal.	12.5	8.4
	7/23/48	Spec. inhal.	10.0	14.0
4	4/29/48	Ragweed	10.0	—
	6/10/48	Ragweed	5.8	3.8
5	1/23/48	Spec. inhal.	33.0	36.0
	9/ 9/48	Spec. inhal.	65.0	16.0
	9/23/48	Spec. inhal.	18.0	11.0
6	2/ 2/48	Feathers	21.4	18.7
7	5/20/48	Ragweed	23.3	10.8
8	6/ 3/48	Ragweed	9.0	8.0
9	6/24/48	Dust	5.6	0
10	7/ 1/48	Ragweed	5.0	0
11	7/ 8/48	Feathers	20.0	10.0
12	7/ 9/48	Ragweed	9.1	9.9
13	7/19/48	Timothy, June grass	23.0	16.0
14	9/ 7/48	Ragweed	5.0	0
15	9/10/48	Ragweed	5.4	3.4
16	9/24/48	Ragweed	0	0

Values are in terms of micrograms of histamine phosphate per 100 ml. blood.
1.0 ml. 1:33 pollen and 1.0 ml. 1:100 dust were used in incubation as indicated.

Histamine may have effects which further complicate the picture of allergy, particularly that of asthma, since it constricts the pulmonary artery and diminishes lung volume. Epinephrine which counteracts the bronchospastic action of histamine would tend to increase pulmonary artery contraction. It is possible that such a mechanism is at play in epinephrine refractory cases of asthma. This has therapeutic implications, i.e., the use of adrenolytic drugs in conjunction with epinephrine, since they reverse its effects only when epinephrine has motor activity.

Our observations on the effect of specific allergens on bloods of allergic subjects are far less spectacular than those reported by Katz and Cohen. Further information on this subject is needed since their work has been extensively quoted as support for the theory that the elaboration of histamine is the cause of symptoms in allergic individuals. We have also noted a consistently lower histamine blood level in allergic subjects in the summer months than in winter. Since bound histamine also most likely reflects the prior presence of free histamine, a low level of their combined values in summer, when allergens are more prevalent in the air, at least suggests that systemic symptoms other than the local effects, such as in hay fever, are not due to histamine unless it is assumed that allergic subjects are more susceptible to it at certain seasons when, perhaps, the threshold of the trigger mechanism is lowered.

Summary

1. Cholinesterases are present in normal amounts in both active and latent allergic states. Their importance is discussed. Certain other blood factors do not parallel them, quantitatively.

2. In the allergic subjects herein considered no such spectacular increments in histamine, as found by Katz and Cohen following incubation of bloods with specific allergens, were demonstrable. This work needs further amplification.

3. The place of the vegetative nervous system and of histamine in the induction of allergic phenomena is discussed.

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RESPIRATORY IMPAIRMENT AND PULMONARY COMPLICATIONS IN PARALYZED STATES: A METHOD FOR EARLY DETECTION*

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Pulmonary atelectasis and pneumonia are common fatal complications of stuporous, debilitating and paralyzed states. In some neurological conditions in which this is apt to occur, notably multiple neuritis, such a complication may be the only cause of death in an otherwise completely recoverable condition. Pasteur [1] attributed the atelectasis in patients with diphtheritic polyneuritis to paralysis of the respiratory muscles, which allowed the lungs to collapse as the result of their normal elasticity. These and other factors are: (1) a reduction of lung volume and constriction of the smaller air ways, as the result of collapse of the chest cage and elevation of the diaphragm, (2) hypoventilation followed by hypoxia and hypercapnea, which result in an increased secretion of mucus into the narrowed airways, and (3) a failure of clearing of the airways by the mechanisms of coughing and vigorous breathing. These factors combine to cause obstruction of smaller airways and produce scattered areas of lobular atelectasis which have the tendency, if not checked, to increase in size and number and become confluent. Data bearing on this problem, and a review of the literature, are presented in another paper.[2]

Because of their usual patchy nature, and because shifting of the mediastinum is absent, these changes in their early phases are difficult to determine by physical examination. Because they may be transient and shift from one site to another, they may not be detected at first by roentgen-ray examination. Usually the first indication of trouble is a rapidly developing fever which is not accompanied by a leukocytosis or an increased sedimentation rate. These small atelectatic areas may be quickly re-aerated in their early stages, but once infected they remain a source of sepsis. Penicillin and other bacteriostatic agents delay the onset of infections and retard their progress, but once established in the lungs of debilitated and paralyzed persons they are very refractory to treatment.

It is of great importance to recognize the circumstances which lead to these pulmonary diseases, and to delay their development until the respiratory mechanisms have recovered. Pasteur [1] pointed out that in diphtheritic polyneuritis this complication could be identified clinically by the presence of (1) increased movements of the lower ribs, (2) reversed movements of the epigastrium during respiration, and (3) altered character of the voice

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and cough. Wilson [3] and Smith [4] used similar clinical criteria for determining the point at which patients with impaired respirations, resulting from acute anterior poliomyelitis, were to be placed in the Drinker respirator. Unfortunately, these methods are not sufficiently sensitive to enable one to identify the milder degrees of respiratory embarrassment producing pulmonary atelectasis but not accompanied by labored breathing and cyanosis.

Obviously a more sensitive and readily applicable method is needed for early recognition of the respiratory embarrassment, leading to atelectasis. Drinker and McKhann [5] recorded the respirations graphically in one patient with acute anterior poliomyelitis. They observed that the occasional deep breaths which occur during mild respiratory embarrassment were absent later just before they considered it necessary to place their patient in the respirator. By a similar method, this series of events has been recorded in the present study, and other observations have been made by which one can identify slight degrees of respiratory embarrassment not detectable by clinical examination alone. It will be shown in this paper that it is possible thereby to detect the predisposing factors in advance of the development of atelectasis.

Material and Methods

Five patients with severe respiratory impairment, the result of paralysis, were studied. In each, the chest was examined clinically and breathing tested frequently with a Benedict-Roth basal metabolism machine. After three to five minutes of quiet normal breathing (tidal air), a series of deepest breaths possible ("vital capacity") was taken. The first of these deep breaths probably approached the true vital capacity of the patient for that time. The vital capacity of the fifth patient was determined daily. Frequent chest roentgenograms (mostly portable) was taken to determine the condition of the lungs.*

Results

The first case illustrates the changes in the respirogram during the development of respiratory failure.

Case 1. A 61 year old Jewish woman with known diabetes for 13 years entered the Boston City Hospital on April 28, 1947, and died September 27, 1947. On the morning of admission she was stricken with severe pain and weakness in the neck and both arms. The pain lasted about 30 minutes. In the next hour and one-half she became quadriplegic. *Examination* revealed a complete paralysis of all extremities and of the trunk. All tendon reflexes were absent and both plantar responses were extensor. Touch, pain, and temperature sensitivity were lost below the sternal notch, but vibration and position senses were present.

The cerebrospinal fluid pressure was 150 mm. of water, and the dynamics were normal. The total protein was 29 mg./100 c.c.; there were no cells. The cervical spine was normal by x-ray examination except for minimal hypertrophic arthritis. A

* I am indebted to Dr. Magnus I. Smedal for reviewing the x-rays with me.

clinical diagnosis was made of thrombosis of a segment of the anterior spinal artery at the cervical fifth and sixth level.

Supportive care, penicillin, and nasal oxygen were instituted on the first hospital day, but the patient developed labored breathing and cyanosis with little change in the frequency of breathing and was placed in a Drinker type of respirator at the beginning of the third hospital day. For the next seven days she was in the respirator for 8 to 12 hours each day. Respiration then recovered sufficiently to discontinue the mechanical aid. On the first hospital day a portable x-ray revealed marked elevation of the diaphragm on both sides and a shadow in the left lower lung field which gradually cleared during the next nine days. The shadow in the lung was interpreted as due to atelectasis. During this time the patient's temperature rose daily to approximately 100° rectally, and on the second and eighth days the white blood counts were 9100 and 10,700, respectively. Thereafter, the patient's temperature remained normal until bedsores and sepsis developed on about the ninetieth hospital day. A swinging temperature was present from then until her death on September 27, 1947. The patient remained quadriplegic throughout the course of her illness, but respiratory paralysis, sufficient to require the aid of a respirator, was absent after the first nine days of her illness and until several days before she died.

During the early part of the illness the patient's breathing was measured repeatedly by a Benedict-Roth basal metabolism machine. Passive breathing, while in the respirator, was also determined frequently to ascertain the efficiency of the machine. During the week that the respirator was used periodically the efficiency of the patient's breathing was maximal immediately after she was removed from this apparatus, and then failed gradually during the hours of voluntary breathing outside the respirator. These changes were clearly indicated in the respiratory tracings and are shown in figure 1, taken on the seventh, and morning of the eighth hospital days. The patient had been in the respirator for 12 hours just before tracing (A) was recorded. Notice the marked variability of the respirations and the periodic deep breaths. The tidal air (exclusive of these deep breaths) varied from about 300 to 400 c.c. The depth of breathing varied in rhythmical cycles, gradually increasing from 300 c.c. to about 400 c.c. and then gradually falling off to 300 c.c. again. Periodic deeper breaths, of about 500 to 700 c.c., occurred from time to time. These appeared to be an exaggeration of the normal variability of the tidal air. At the end of the record the patient was asked to take a series of deepest possible inspirations. These are underlined in this and all other tracings by a solid black line. In this instance these inspirations were at first 900 to 1000 c.c. and then fell off to about 500 c.c. The patient was comfortable and her breathing appeared normal. Eight hours later a second tracing (B) was recorded. Note that the tidal air was still variable, but somewhat less (200 to 325 c.c.) than in tracing A. Also the periodic deeper inspirations were absent. Her deepest breaths were reduced to a maximum of about 525 c.c., and succeeding deep breaths fell rapidly to a much lower figure. The patient was still comfortable and not cyanotic. Although it was recommended, the patient objected to the respirator at this time. Two hours later she was slightly cyanotic, and dyspneic, and tracing C was taken. Note the uniformity of the tidal air which now averaged about 240 c.c. Also note that the deepest possible inspirations were only slightly greater than the tidal air (about 300 c.c.) The patient was then placed in the respirator for the night. Tracing D was taken the following morning just after the patient was removed from the respirator. The respiratory function was clearly improved. The tidal air averaged from 300 to 400 c.c. again and frequent deep breaths, as great as 600 c.c., were present. Her deepest breaths were approximately 900 c.c. After the tenth hospital day when the patient had recovered sufficiently to get along without the respirator her breathing was periodically checked. The tidal air varied rhythmically from 300 to 400 c.c., and there were periodic deep breaths of

500 to 700 c.c. volume. The deepest never exceeded 1000 c.c. During the last three days of life her respirations failed again and were attended by changes identical to those shown in figure 1.

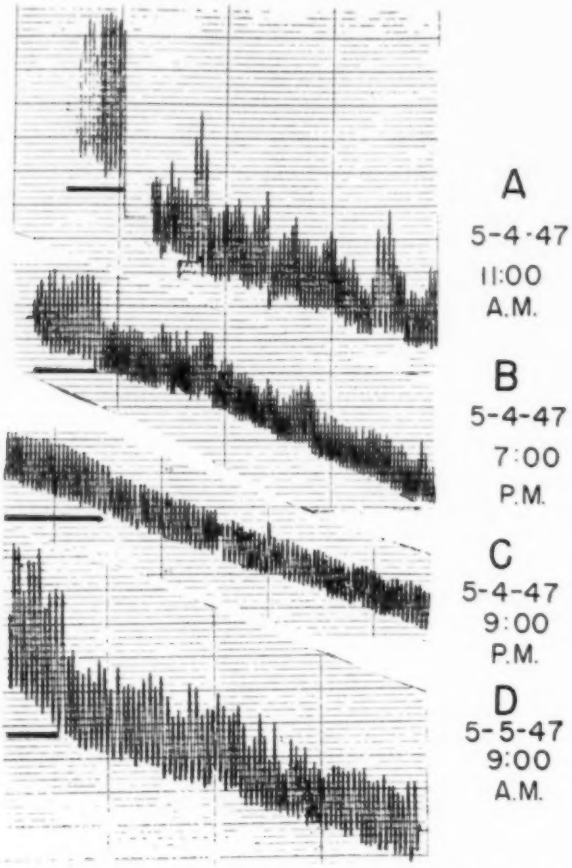

FIG. 1. A series of respiratory tracings in case 1. Tracings A, B, and C were taken on May 4, 1947, and D on the following day. The time of each tracing is noted opposite each tracing. Tracings A and D were taken shortly after the patient was removed from the respirator. For detailed descriptions of each tracing see the text. The deepest-possible breaths are underlined by a solid black line in this and subsequent figures.

The series of respiratory tracings shown in figure 1 illustrate the changes in character of the breathing during respiratory failure which were observed in this patient several times. The seriousness of the patient's respirations was not clearly evident on clinical grounds alone until just before tracing C was taken, yet it was quite apparent from the breathing tests that the respiratory function was impaired in tracing A, and that respiratory failure was imminent when tracing B was taken.

The next three patients did not survive. An analysis of their first breathing records showed evidences of severe respiratory impairment in the second and third cases. Respirations had failed in the fourth patient to a degree that made it impossible to test his voluntary breathing.

Case 2. A white, married female, 26 years old. During the week preceding entry to the hospital the patient developed weakness and then paralysis, first of both legs, and then the trunk and upper extremities. This was accompanied by numbness of the peripheral parts of the extremities.

Examination revealed shallow abdominal breathing, almost complete paralysis of all four extremities, and bilateral paralysis of facial muscles below the brow. There was reduced sensitivity to cotton below the knees, and impaired vibratory and position sense in both legs and feet. Tendon reflexes were absent. The spinal puncture revealed an initial pressure of 250 mm. of water, normal dynamics, total proteins of 666 mg./100 c.c., and 2 lymphocytes. The white blood count was 9800, differential count was normal and the blood Hinton test was negative. The diagnosis was considered to be infectious polyneuritis. This was confirmed post mortem.

Supportive care, penicillin, and nasal oxygen were instituted on the first hospital day. On the second hospital day, respiratory distress became evident and the patient was placed in the respirator. The temperature rose rapidly and ventilation by the respirator became progressively less effective. The patient died on the fourth hospital day.

Records of her respirations are shown in figure 2. Tracings A and B were taken during the afternoon of the day of entry to the hospital. The patient was supine during both tracings. In tracing A the head of the bed was elevated about 20 degrees above the horizontal and in tracing B the bed was level. The interval between records was only a few minutes. With the head of the bed slightly elevated (A) the average tidal air was about 300 c.c. When flat it was about 250 c.c. In tests in other patients as well, the tidal air was usually increased by elevating the head about 20 degrees. This often relieved dyspnea which was present when the patient's head was not elevated. Furthermore, depressing the head below the horizontal interfered with their breathing. Note that the tidal air in both tests was almost uniform in amount, that the occasional deep respirations were absent, and that the deepest possible inspirations were only 500 to 600 c.c. The patient was comfortable and not cyanotic. The next morning the patient suddenly became dyspneic and was placed in the respirator at once. A short breathing test, just before the patient was placed in the respirator, revealed no occasional deep breaths, only a slight variation in the tidal air which averaged 225 c.c., and deepest breaths possible of 275 to 300 c.c. Unfortunately, this ink record was smeared and the patient's condition was too critical for another test at this time. Another respiratory test could not be obtained until the next day (tracing C). This record shows a uniform tidal air of less than 200 c.c. and attempted deep breathing could not increase this. Tracing D was taken shortly after tracing C with the patient back in the respirator. It is a record of ventilation of the lungs produced by the respirator. Each respiration averaged 450 to 500 c.c. Seven hours and 20 minutes later this was repeated (tracing E). Each tidal air averaged about 350 c.c. and all attempts to increase the amount, including the insertion of an airway, failed. The patient died the following morning.

An autopsy revealed massive atelectasis of the left lung, and bronchopneumonia which was moderately extensive in the right middle and left lower lobes, and very severe in the right lower lobe. There was also bilateral pulmonary congestion and edema. The clinical diagnosis of infectious polyneuritis was confirmed.

Case 3. A 58 year old single white male. About six days before admission the patient developed a mild upper respiratory infection. On the day of admission to

the hospital, weakness appeared in the legs and within a short time progressed to involve the arms and hands. *Examination* revealed marked flaccid weakness of all extremities, and reduced sensitivity to pin prick of the legs and arms. The lumbar puncture pressure was 110 mm. of water, dynamics were normal, protein was 30 mg./100 c.c., and there were no cells. The Wassermann test was negative. The white blood count was 6500 and the differential count normal.

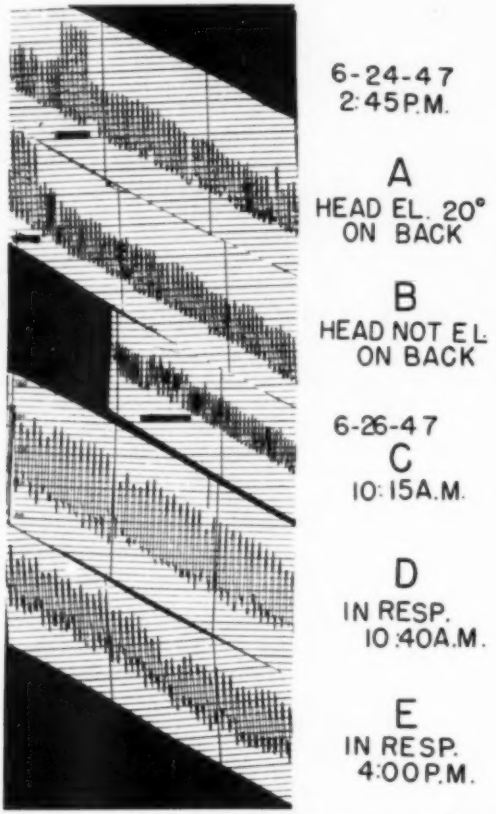

FIG. 2. A series of respiratory tracings in case 2. Tracings A, B, and C are records of voluntary breathing. Tracings D and E are records of the ventilation produced by the respirator. The date and time of day are indicated opposite each tracing.

The weakness increased and by the fourth day both arms and legs were almost completely paralyzed. His respirations, however, were not labored and he was not cyanotic. On the following day he rapidly developed dysphagia and hoarseness, his breathing became labored, and his extremities cyanotic.

His breathing was tested shortly after the development of respiratory difficulty, and the patient was then placed in the respirator. The pre-respirator tracing is shown in figure 3, A. The tidal air averaged about 525 c.c., there were no deep

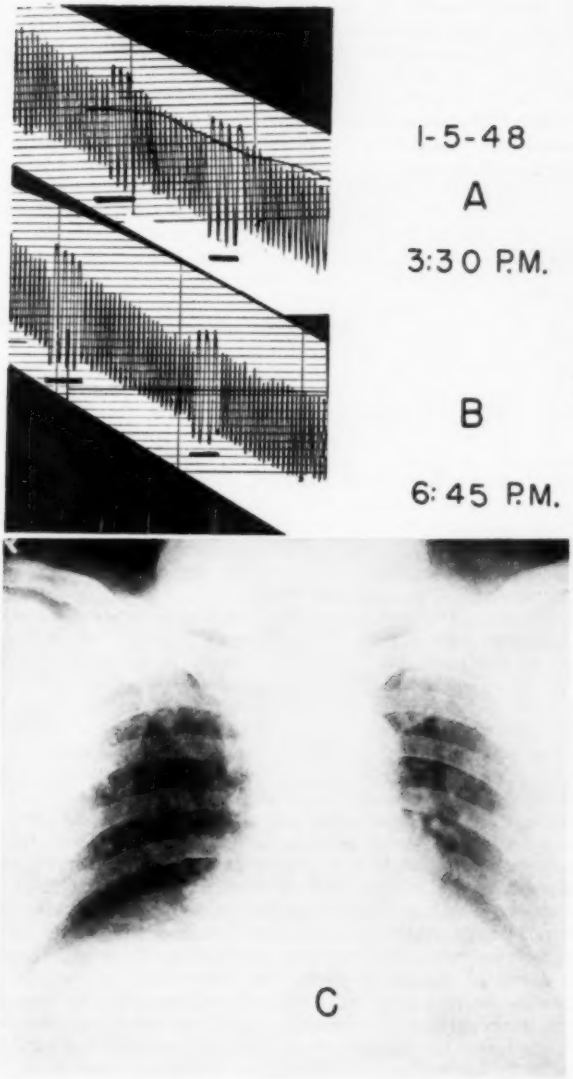

FIG. 3. Respiratory tracings and one portable x-ray for case 3. Tracings are labeled as in previous figures. The x-ray (C) was taken just before tracing B was recorded.

breaths, and the rhythmical rise and fall of the tidal air volume shown in figure 1, A, B, and D was absent. Despite the normal tidal air volume, the patient could increase the depth of his breathing to no more than 600 c.c. Three hours and 15 minutes later (tracing B) the tidal air and deepest breaths were both diminished slightly. An x-ray taken just after tracing B (figure 3, C) revealed a very dense right paracardial shadow and elevation of the right leaf of the diaphragm. This was interpreted as atelectasis. There was also considerable clouding of the left base, which was probably due to atelectasis, with superimposed pneumonia, although from the uniformity of the density, a pleural effusion could not be ruled out. The ventilation accomplished by the respirator gradually lessened and the patient died the following morning.

Case 4. A 52 year old white male. Following a sore throat and cough of a week's duration this patient became hoarse and able to speak only in a whisper the day before admission. *Examination* revealed absent biceps and ankle jerks and an injected throat. Muscular weakness was not noted at this time. The lungs were normal to physical examination.

During the first week in the hospital the patient's temperature dropped slowly from 102° to normal. An x-ray on the third hospital day showed right upper and lower lobe bronchopneumonia. On the fourth hospital day he became confused, disoriented, and difficult to handle. He was given penicillin and sulfadiazine and his temperature returned to normal. He became symptom free, except for marked weakness. On the twenty-second hospital day the patient complained again of marked hoarseness and weakness. On the thirty-third day he was unable to stand and seven days later bilateral facial weakness, paralysis of the left vocal cord, and moderately severe emaciation were noted. At this time the cerebrospinal fluid was normal. On the following day (forty-first day) slight and transient dyspnea was noted for the first time. The next day his respirations rapidly failed and cyanosis developed. The patient was then placed in the respirator. The diagnosis in this case was multiple neuritis, type undetermined.

Tracings of this patient's voluntary breathing could not be obtained, because of his critical condition, but a series of respiratory tracings and x-rays was taken while he was in the respirator. These are shown in figure 4. Shortly after he was placed in the respirator (6:00 p.m.) a portable x-ray of the chest (figure 4 E) was taken. This x-ray showed "shingling" of the ribs on the right, and general under-aeration of the right lung. There was a slight shift of the mediastinum to the right without elevation of the diaphragm and a sharply defined density in the cardiophrenic angle. This was interpreted as a segmental collapse of a right base with partial atelectasis generally in the right lung. A day later another x-ray (figure 4 F) revealed a marked increase in the size and density of the shadows in the right lung and the appearance of dense areas in the left lung with a very high diaphragm. The findings were interpreted to indicate that some pneumonia was present, but the rapid development of the process and its segmental nature indicated that it was largely atelectasis. The increasing consolidation of the lungs was reflected in the breathing tests by a gradual decrease in the amount of air entering the lung with each cycle of the respirator. In tracing A, the ventilation averaged about 550 c.c. per cycle. This decreased steadily to slightly over 300 c.c. in tracing D. The patient died the following morning at 8:45 a.m. The irregular breathing illustrated in tracing C was due to struggling of the patient. This lack of coöperation or inability to breathe with the respirator was common in very sick patients, and occasionally could be overcome by increasing the cycle frequency of the respirator (tracing B) or by morphine (tracing C).

The following patient recovered and illustrates a method of treating pulmonary atelectasis which appeared to be helpful.

Case 5. A 48 year old white male. Three weeks before admission to the hospital the patient developed weakness and numbness of both legs which progressed to involve the trunk, both upper extremities, and the right lower facial muscles. Diplopia was present for a short time. The condition was progressive for one week and then remained fairly stationary for another two weeks. Upon admission to the hospital all tendon reflexes were absent. Pain and touch sensitivity were reduced in the periphery of the extremities, and position and vibratory sense were absent.

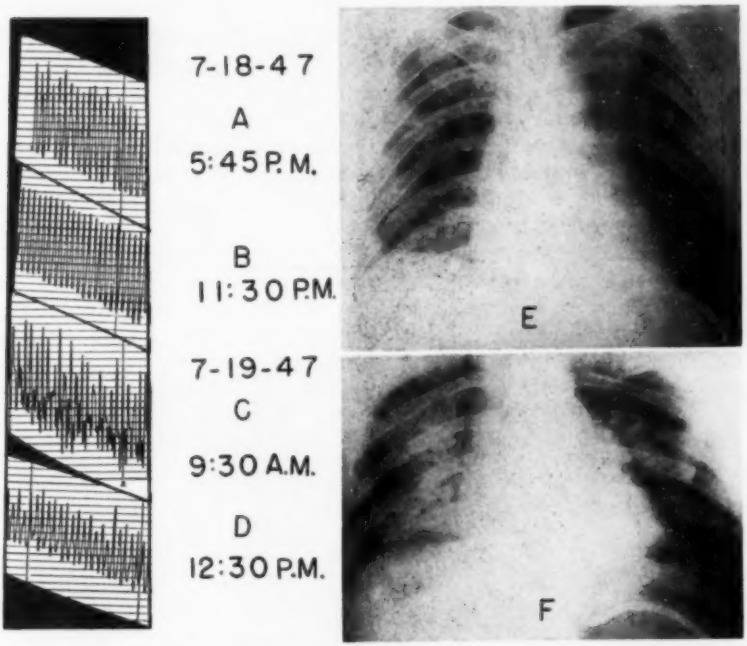

FIG. 4. A series of respiratory tracings (A, B, C, and D) and two portable x-rays (E and F) in case 4. The tracings were taken with the patient in the respirator, and record the ventilation produced by this apparatus. E is a portable chest x-ray taken just after tracing A, and F was taken the afternoon of the following day.

The cerebrospinal fluid pressure was 130 mm. of water, dynamics were normal, the protein content was 308 mg./100 c.c. and there were no cells. An x-ray of the lungs was normal. The clinical diagnosis was infectious polyneuritis. The clinical course in this case is shown in figure 5.

His vital capacity on the third hospital day was 900 c.c. A breathing test on the fourth hospital day revealed an average tidal air of 370 c.c., with normal variability in depth, and occasional deep breaths of 500 to 600 c.c. The vital capacity increased steadily to reach 1700 c.c. on the seventh day. On the ninth day his rectal temperature rose to 101.6°, and the vital capacity dropped to 1000 c.c. At this time an x-ray of the chest (figure 5, B) showed an increased density at the left base with elevation of the left leaf of the diaphragm and narrowing of the left intercostal spaces,

which was considered consistent with atelectasis. The following additions were made to the management: every four hours the patient was assisted to a sitting posture, and his vital capacity determined. In the next seven days his vital capacity increased to 2200 c.c., his temperature fell to normal, and the density in the x-ray cleared. Four days after the x-ray shown in figure 5, B another x-ray of the chest (figure

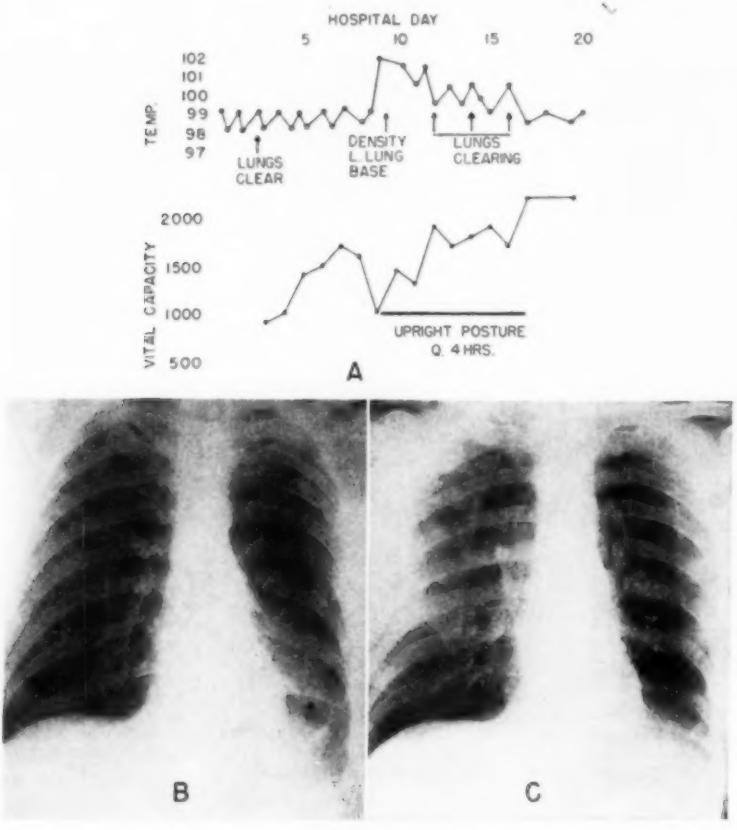

FIG. 5. A clinical chart of the rectal temperature, vital capacity, x-rays, and duration of postural treatment (A), and x-rays taken on the ninth (B), and thirteenth (C) hospital days. Note the elevation of left half of diaphragm (indicated by arrow) in B, and residual clouding at left base in C.

5, C) revealed marked clearing in the left chest with return of the left leaf of the diaphragm to a near normal level. Four days later further clearing had occurred, and a small amount of fluid remained in the left pleural space, suggesting that some pneumonitis with pleuritis was present. The patient gained strength rapidly, and on the sixty-fifth hospital day was able to walk.

Discussion

In this section the following points will be amplified:

1. The clinical aspects of the five cases just presented, stressing the apparent abrupt onset of respiratory impairment, and the difficulty and need for its early diagnosis and treatment.

2. A method of recognizing respiratory impairment prior to the development of pulmonary atelectasis.

3. The probable mechanisms of the respiratory changes.

The cases presented in this paper demonstrated three important clinical facts. First, by means of physical examination alone early respiratory impairment is very difficult to diagnose; it was not recognized in any of the five cases. Transient labored breathing was observed in several cases, but this had disappeared when the patient's position had been changed, and the observation had been misinterpreted or overlooked. It appears that transient dyspnea indicates a grave prognosis in cases of this type. Second, although the clinical evidence of respiratory failure appeared to develop very acutely, respiratory measurements revealed striking indications of impaired respiratory function many hours, or even a day before. Third, when respiratory impairment was recognized clinically pulmonary atelectasis was probably present in all five cases; it was demonstrated by x-ray examination in four cases, and postmortem examination indicated that it had been present in the fifth.

The pulmonary changes were apprehended early in case 1 and reëxpansion of what was probably atelectasis alone was accomplished during the period of treatment in the respirator. In this patient severe respiratory embarrassment with labored breathing and cyanosis developed several times, yet the pulmonary complication was controlled, and the lungs were reexpanded. It is significant that the duration of severe pulmonary impairment in this case was of short duration and periodic. On the other hand, impaired respiratory function (without labored breathing and cyanosis) had existed continuously for 24 or more hours in the three fatal cases (2, 3, and 4) before the respirator was employed. The respiratory, x-ray, and postmortem studies indicated that despite penicillin, sulfadiazine, and the mechanical respirator, the pulmonary complications were not controlled, and other parts of the lungs became involved. These observations suggest that if the conditions which lead to the pulmonary complications are recognized early, and severely impaired respiratory function has not developed or has existed for only a few hours, the respirator can be life saving. In contrast, if the pulmonary complications have been present for a day or longer, then atelectasis with superimposed pneumonitis will very likely spread in spite of the respirator. The presence or absence of superimposed infection may determine whether an area of atelectasis can be reëxpanded in the respirator.

In patient 5 the pulmonary complication developed during the period of recovery when the respiratory function was considered adequate. It is

possible, however, that he had a pulmonary infection before, or during, the first few days in the hospital, since his leukocyte count was elevated. This may have been a factor in precipitating atelectasis when the circumstances which ordinarily produce it were on the wane. The postural treatment with deep breathing seemed to influence this complication favorably. Essentially the same method has been used by us before to reëxpand small patches of atelectasis in deeply narcotized patients.[3]

Although the respiratory function in case 5 improved steadily during the first week in the hospital, it is not unlikely that periodic "rests" in the respirator would have benefited his breathing and prevented the development of atelectasis. The breathing in case 1 was obviously benefited by this procedure; the average tidal air and vital capacity increased, and rhythmical breathing and occasional deep breaths returned after a period of 8 to 12 hours in the respirator. In all probability the improved spontaneous breathing was more beneficial than the action of the respirator itself in reëxpanding the atelectatic lung in this case. It is quite likely that the periodic use of the respirator prior to the development of respiratory failure would improve the outlook of patients with impaired respirations and in some cases obviate the continuous use of this apparatus later in the course of the disease.

During the development of paralysis of the respiratory mechanisms, the following progressive changes were observed in graphic records of the respirations made with the Benedict-Roth apparatus:

A. The vital capacity (or deepest possible breaths) and tidal air became reduced to approximately 1000 and 350 c.c., respectively.

B. Rhythmical variations in the depth of the tidal air and periodic deep breaths of 500 to 700 c.c. appeared in the respiratory records.

C. The periodic deep breaths disappeared. Atelectasis occurred after this development. This raises the question of whether the periodic deep breaths helped to prevent atelectasis by frequent aeration of the less ventilated areas of lung tissue. From our few observations, this would appear to be the latest stage at which patients with failing respiration should be placed in the respirator.

D. The rhythmical alterations in the depth of breathing disappeared, and the tidal air became uniform in amount at between 220 and 250 c.c., and could be increased very little if at all by maximum effort. This stage was accompanied by labored breathing and cyanosis, and by a rapid failure of the respirations.

The series of changes just described are shown schematically in figure 6. The factor of time varies from hours to a number of days. The other variables are indicated by dashed lines.

There can be little doubt that the initial decrease in tidal air and vital capacity were due to the weakened or paralyzed muscles of respiration. The variation in depth of the tidal air and the occasional deep breaths are less easily explained. Similar variations in respirations have been produced

in normal subjects by hypoxia,[6] and by fatigue of the respiratory mechanisms.[7] Since these factors operate during progressive paralysis of the respiratory muscles, it is not unlikely that they were responsible for the irregular breathing in the cases reported in this paper. Fatigue was probably the more important factor since the irregularity was not significantly reduced by continuous nasal oxygen (5 to 7 liters/minute), nor by breathing 100 per cent oxygen for 5 to 10 minutes during a respiratory test as it was observed to do in the normal subjects of Haldane, Meakins and Priestley.[6] The subsequent disappearance of the irregular breathing in the five cases reported here suggests that the fatigue of the respiratory mechanisms had become even more marked, finally to the degree that each breath was a maximal one.

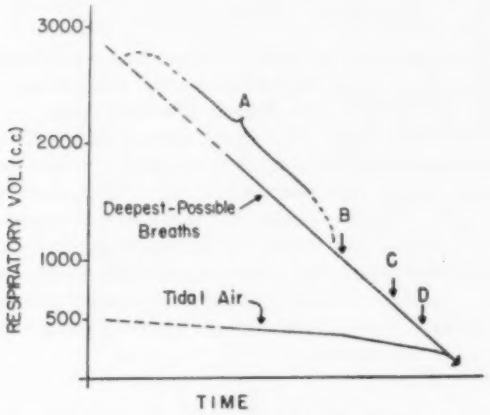

FIG. 6. The changes which occur during the development of respiratory impairment schematically. The diagram is explained more fully in the text.

No proved explanation of the abrupt onset of dyspnea can be given. Probably it is related to hypercapnea which develops as the result of hypoventilation.[8] Hypoxia may also be a factor, but it is probably of less importance, as cyanosis often appeared after labored breathing had been present for some time. This observation cannot be considered final since the oxygen content of the arterial blood was not determined. It is not surprising that the labored breathing from an increase in the carbon dioxide content of the blood occurs acutely, since a desire to breathe deeply is produced by very small increases of this substance. A rapid development or increase of atelectasis would seem adequate to produce hypercapnea. It is also quite possible that a time arrives during the development of respiratory failure when the respiratory reserve is minimal, and the ventilation is not quite adequate to prevent a rise in the carbon dioxide content of the blood. Because the respirations cannot be increased in a normal manner, a subjective sense of suffocation occurs.

The mechanism of the fever without other evidences of infection (leukocytosis and an increased sedimentation rate) in patients with atelectasis was observed and discussed before.[2] It was suggested that this was due to a reduced loss of heat by way of the lungs, the result of hypoventilation, and from the skin, because of peripheral vascular failure. It is interesting that although the temperature usually drops during the first few hours of barbiturate narcosis, in pentothal narcotized dogs made apneic by tracheal infusion of 100 per cent oxygen, the temperature has been observed to rise an average of 0.5° in less than one hour.[9] This would tend to support the suggestion that a failure of heat loss through the lungs may be a factor in producing a fever in these patients.

Summary and Conclusions

The respirations of five patients with seriously impaired respiratory function were measured frequently with a basal metabolism machine, and the tidal air and vital capacity (or deepest possible breaths) were recorded. By this means, significant degrees of respiratory impairment were detected before they were recognized by clinical examination. It is important that respiratory impairment be recognized early since pulmonary atelectasis, and sometimes pneumonia, develop before the respiratory function is obviously embarrassed. If patients are placed in the respirator after both of these complications have developed the course of the pulmonary condition is apt to be progressive to death. If recognized early, and the respirator is employed part or full time, before or soon after atelectasis has developed, the outcome should be more favorable.

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CLINICAL PATTERNS OF MYOCARDIAL INFARCTION IN AMBULANT PATIENTS*

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Introduction

While attending an outpatient diagnostic clinic serving a labor union whose membership consists of industrial workers, we were surprised by the relative frequency with which we saw electrocardiograms indicative of old or recent myocardial infarction in patients who had no history of any acute disabling cardiac episode. The classical concept of coronary occlusion and myocardial infarction as a dramatic clinical picture, with an abrupt and terrorizing onset of excruciating pain, dyspnea, angor animi, and collapse, and the usual physical and laboratory concomitants such as fever, gallop rhythm, friction rubs, leukocytosis and elevated sedimentation rates, has been modified in recent years by an appreciation of the evidence that infarction may occur without occlusion,[1] that occlusion may occur without infarction,[2] and that infarction may occasionally occur without symptoms of sufficient severity to disturb the patient.[3]

The incidence of painless myocardial infarction has been variously reported as occurring in as low as 4 per cent to as high as 61 per cent of all myocardial infarctions.[3] The difference in the reported incidence of painless myocardial infarction is influenced by rather arbitrary opinions as to what degree of discomfort may constitute pain, or by the degree of shock and/or dyspnea which might mask pain. Reviews based solely upon autopsy material similarly exhibit wide differences in incidence of painless infarction.[3]

Since most clinical and pathologic studies of myocardial infarction have dealt with hospitalized patients, it was felt that the incidence of painless and asymptomatic myocardial infarction could be better approximated by studying a gainfully employed group using the electrocardiogram as the diagnostic index. These patients are members of a large labor union whose jobs run the whole gamut of the physical requirements necessary in industry. All of the patients were ambulatory.

Material and Method

The entries of the past two years in the electrocardiographic files under the heading of "Myocardial Infarction" were reviewed and 110 cases were selected consecutively, the only basis of the selection being that the electrocardiograms were unequivocally characteristic of old or recent myocardial

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infarction. The diagnostic electrocardiographic patterns of infarction are described in standard textbooks [4] and need not be reviewed here. Tracings which were only suggestive of infarction were excluded. Non-specific patterns were excluded; for example, ST segment depression and T wave changes in precordial leads in positions 5 and 6, and the standard Lead I may be the only electrocardiographic abnormalities encountered in the usual leads in even fatal infarction of the septum or lateral wall of the left ventricle, or in infarctions limited to the subendocardial tissues; however, such changes may also occur as a result of left ventricular hypertrophy, myocardial anoxemia, or digitalis administration, and since definitive pathologic verification was not available, such tracings were excluded. Because of the difficulty in diagnosing myocardial infarction electrocardiographically in the presence of left bundle branch block, such cases were included only where there were diagnostic changes evident on serial tracings, or where the bundle branch block was transient.

In a few of the earlier records, the diagnosis was based on the three standard leads plus a minimum of two precordial leads (CF_2 and CF_4); however, in the vast majority of cases, the records included the three standard leads, the three augmented unipolar extremity leads (V_R, V_L, and V_F), and a minimum of three precordial leads (V_2, V_4, and V_5). Additional leads from the right side of the chest, the second and third left interspaces, the left axilla, and the back had been taken whenever indicated. Multiple or serial electrocardiograms were available in many instances.

Having selected 100 cases conforming to the criteria outlined above, we reviewed the clinical records of these patients and classified each case in one of the following groups:

A. *Asymptomatic*—Seven patients. This group consisted of those patients with electrocardiographic evidence of infarction who had no symptoms referable to the heart. The electrocardiographs were taken in these patients as an incidental portion of a general medical examination.

B. *Typical*—52 patients. These patients had histories of acute episodes compatible with the classical clinical picture of myocardial infarction, and followed by disability of varying duration. In some of these patients, the symptoms described had not been attributed at the time to an acute cardiac episode, but were recognizable as such in retrospect after the electrocardiographic evidence of infarction was obtained.

C. *Atypical*—41 patients. In this group were patients with symptoms of cardiac insufficiency of varying degrees of severity, but with no history of an acute attack of chest pain which was of sufficient severity to warrant recognition by the patient or his physician as a "heart attack."

The patients in this series came to the clinic primarily for symptoms referable to the cardiovascular or other systems, for general physical examination, or for advice relative to work capacity. As far as could be determined, the myocardial infarctions in these 100 cases were all presumably

superimposed upon arteriosclerotic coronary artery disease, except for two cases in which luetic coronary ostial stenosis may have played a part.

General Features

Age: The group ranged in age from 29 to 70 years at the time of examination, with an average age of 54.6 years. In those patients with histories of acute attacks or with symptoms of circulatory insufficiency (i.e. the typical and atypical groups), the age at onset ranged from 27 to 70 years, with an average of 53.6 years. The age incidence of decades is presented in table 1,

Table I

Age Incidence at Time of Examination

Age	20-29	30-39	40-49	50-59	60-69	70-79
Asymptomatic			2	2	3	
Typical		3	12	20	15	2
Atypical	1	1	7	22	10	
Totals	1	4	21	44	28	2

and deserves no comment other than to note that it agrees with accepted figures. There were no significant differences in the age incidence in the various groups.

Sex and Color: These factors cannot be evaluated in this study, because there were no females in this group, and only one colored male. The clinic population is 14 per cent female, and 6.6 per cent colored.

Associated Diseases: Examination of these patients revealed the customary ailments to which flesh of this age group is heir, and the incidence of some of the associated diseases of major significance is presented in table 2. There were a goodly number of patients with hernias, hypertrophy of the prostate, varicose veins, cataracts, and post-traumatic deformities, as might be expected. The relationship of hypertension, obesity, and diabetes mellitus to coronary artery disease has been amply expounded.

Chest roentgenograms were available for 93 of this group of 100 patients, and the heart was enlarged roentgenologically in 17 of these. Moderate or marked atherosclerotic changes of the aorta were apparent on the roentgen-ray in 13 cases, as gauged by tortuosity, dilatation, and/or calcification of the aorta.

Electrocardiographic Localization of the Infarction

Table 3 demonstrates the relative incidence of the locations of the infarcts as determined by electrocardiography. It is evident that, of the entire series, 62 were anterior or lateral in location, while 38 were posterior (including posterolateral). In the "asymptomatic" group, two were anterior and five posterior. In the "typical" group, 26 were anterior, and 15 posterior.

TABLE II

Incidence of Associated Disease of Major Significance

	No. of Patients
Hypertension	28
Obesity, marked	22
Diabetes mellitus	4
Chronic bronchitis and pulmonary emphysema	3
Cerebrovascular accidents	3
Syphilis, latent	2
Silicosis	2
Peripheral vascular disease	2
Tuberculosis, minimal, inactive	2
Rheumatic heart disease, inactive	1
Hepatic cirrhosis	1
Lung abscess	1
Epilepsy	1
Embolism to leg from mural thrombus	1
Bronchial asthma	1

The relative proportion of anterior to posterior myocardial infarctions in this series is about the same as has been reported in the literature.[5, 7c] There was no marked difference in this ratio in the typical and atypical groups. It has been noted repeatedly that the presence or absence of pain or the severity of the latter cannot be used to estimate either the presence, size, or the location of an infarct.[5, 3a, 7c]

TABLE III

Electrocardiographic Localization of the Infarction

Anteroseptal	26
Anterolateral	15
Extensive anterior infarction	18
Lateral	3
Posterior	36
Posterolateral	2

The incidence of associated electrocardiographic abnormalities is presented in table 4. There were no significant differences in the incidence of these findings in the three groups. In 27 instances, the myocardium was still in the "injury phase" as indicated by abnormal elevation of the ST segments in the leads involved.

TABLE IV

Incidence of Associated Electrocardiographic Abnormalities

Premature contractions (nodal, auricular, ventricular)	14
Intraventricular conduction defect	11
Auriculo-ventricular block, incomplete	7
Sinus tachycardia	6
Auricular fibrillation	2
Right bundle branch block	2
Auricular tachycardia	1
Auricular flutter	1
Left bundle branch block	1
Left bundle branch block, inconstant	1
Digitalis effect	1

The relative values of the standard leads, multiple precordial leads, and unipolar extremity leads in this series were briefly explored. Of the 38 records with electrocardiographic evidence of posterior infarction, the standard leads were diagnostic in all instances, as might be expected from the criteria used. The augmented unipolar lead from the left lower extremity was confirmatory in those instances in which it was available, but it was not used here as the sole index of posterior infarction. In the 62 anterior or lateral infarctions, the standard leads were diagnostic (confirmed, of course, by precordial leads) in only 20 instances (32 per cent), and were entirely normal in only six instances. In 36 instances, the standard leads were indefinite in that Lead I exhibited flat or low T waves and/or questionably significant Q waves as the sole abnormalities. The electrocardiographic diagnosis of anterior infarction therefore depended upon multiple precordial leads in 42 of the 62 cases (67 per cent). Others have reported an incidence of 40 per cent of positive diagnostic evidence in the limb leads in anterior myocardial infarction.[6]

Clinical Features

Asymptomatic Group: This group consisted of seven patients, none of whom had symptoms referable to the heart or a history of an acute "heart attack." Three of these patients came in for general physical examinations. The other four had complaints not referable to cardiac insufficiency. The electrocardiograms were incidental to a general medical examination and revealed unsuspected evidence of infarctions as manifested primarily by abnormal Q waves and residual sharp inversion of the T waves in the pertinent leads. ST segment deviation of significant degree or abnormal contour was rarely apparent in this group. In two patients, the infarcts were anterior, and in five patients posterior in location. Representative cases are quoted below:

Case 1. A 60 year old white male with no complaints came in for a general medical examination. There were no abnormal physical findings. Blood pressure was 134 mm. Hg systolic and 76 mm. diastolic. X-ray of the chest showed tortuosity and elongation of the aorta, and slight bronchovascular accentuation. The electrocardiograph showed first stage auriculo-ventricular block (P–R interval = 0.24 sec.), an occasional auricular premature contraction, a QS complex in V_2 with slight elevation and upward convexity of the ST segment and inversion of the T wave, a small Q wave in V_4 with a coved ST segment, and an inverted T wave, and diphasic T waves in V_5 and aV_L, findings which were consistent with old antero-septal infarction (see figure 1).

Case 2. A 52 year old white male came in with complaints referable to peripheral arteriosclerotic vascular disease. He had a history of a right hemiplegia secondary to a cerebrovascular accident two years previously, with subsequent partial recovery of function. There were no symptoms of cardiac insufficiency. Physical examination revealed slight obesity, residua of old right hemiplegia, diminished pulsations in the vessels of the lower extremities, and a blood pressure of 170/90. Chest x-ray was normal. The electrocardiograph showed deep Q waves with inverted T waves in Leads II, III, and aV_F, consistent with old posterior infarction.

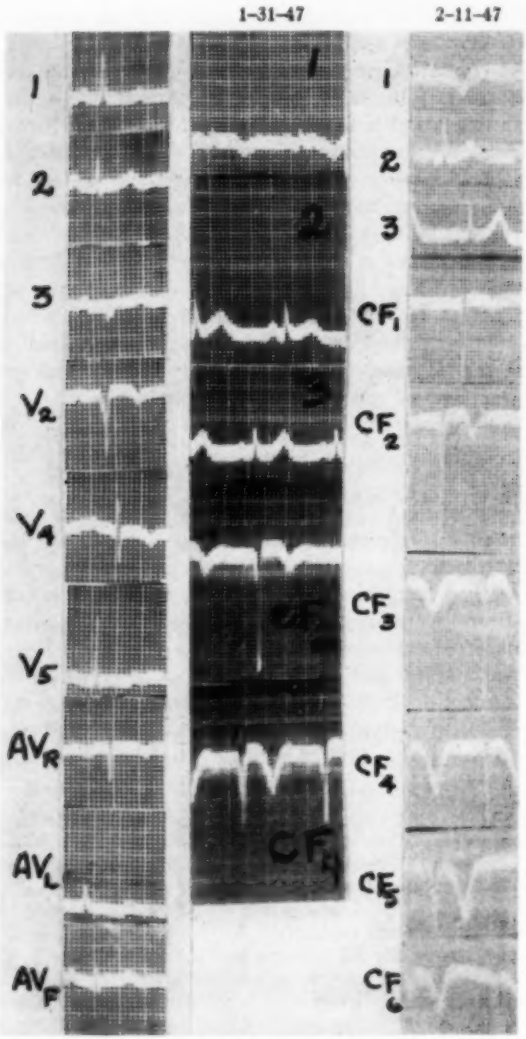

FIG. 1. Case 1. FIG. 2. Case 3.

Typical Group: This group was labeled "typical" because the patients had histories of one or more episodes which conformed to the classical clinical picture of coronary occlusion. There were 52 patients in this group, four of whom had had one previous attack. The severity of the symptoms at

the time of the acute episode varied greatly, and in many instances the diagnosis became apparent in retrospect when electrocardiographic studies were done. Several of these patients previously had been treated for gall-bladder disease, peptic ulcers, "chemical poisoning," respiratory diseases, and the other afflictions which enter into the differential diagnosis of coronary arteriosclerosis and its complications.

The intervals which had elapsed between the acute attack and the time of examination in the 56 infarctions represented in this group of 52 patients were distributed as follows:

Less than 1 week	4 cases
1 to 2 weeks	3 cases
2 weeks to 1 month	3 cases
1 month to 6 months	20 cases
6 months to 1 year	11 cases
More than 1 year	15 cases

The shortest interval was two days, and the longest was eight years.

Because of the varying intervals since the infarction, a detailed review of the symptoms and signs in this group would serve no purpose; however, brief mention may be made of the extent of disability as gauged by the histories. Accustomed as most of us are to prescribing relatively long periods of bed rest to patients with myocardial infarction, it was surprising to us to find that of 14 patients with typical histories of infarction occurring within two months prior to date of examination, seven patients had either continued working or had returned to work after one or two days' rest at home. Of the entire group of 52 patients, only 21 had exertional angina and only one had angina at rest, and of these only three were so disabled by the angina that they were unable to work. Ten complained of exertional dyspnea not necessarily associated with angina. Five patients had intermittent episodes of abdominal, neck, or upper extremity pain which were interpreted as atypical angina. Three patients were in mild congestive failure at the time of examination, although they were still working on a full-time basis. The electrocardiographs indicated posterior infarction in 18 patients in this group, and anterior or lateral in 34 patients. The electrocardiographs of seven patients were still in the "injury" stage at the time of examination as evidenced by significant elevation and abnormal contours of the ST segments in the pertinent leads.

Representative cases are quoted below:

Case 3. A 35 year old colored male was seen on January 31, 1947. Eleven days previously, immediately following lunch, the patient developed lightheadedness, nausea, and vomiting. After emesis, he noted severe squeezing retrosternal pain radiating through the chest to the interscapular area, associated with dyspnea. The vomiting subsided in one-half hour, but the pain persisted in diminishing degree for one week. Because the patient was exposed to magnesium fumes, his symptoms were interpreted by his physician as resulting from "chemical poisoning." At the time of examination,

the blood pressure was 110/70. There was a split second sound at the pulmonic area and a short blowing systolic murmur at the base, maximal at the pulmonic area and transmitted to the aortic. The sedimentation rate was 26 mm. in an hour (Cutler method). The chest x-ray indicated that the heart was at the outer limit of normal in size. The electrocardiograph showed sharp inversion of the T wave with elevation of the ST segment and low voltage of the QRS complex in Lead I, and QS complexes and sharp inversion of the T waves in Leads CF_1 through CF_4, findings consistent with recent extensive anterior infarction (figure 2).

Case 4. A 61 year old white male was seen on August 12, 1947. One week prior while at work, he developed severe retrosternal "cutting" pain radiating to both shoulders and down both arms, associated with profuse perspiration. He was taken to the plant hospital where he remained for two and one-half hours and then went home. He remained at home but was up and about, during the ensuing week, with his only difficulty being dyspnea on recumbency, with resultant insomnia. Physical examination revealed an acutely ill male with marked dyspnea. Blood pressure was 110/90. There was a large abdominal incisional hernia, but the examination was otherwise not remarkable. X-ray of the chest showed generalized cardiac enlargement probably due to dilatation. There was a slight leukocytosis with a normal differential. The sedimentation rate was elevated to 24 mm. in an hour (Cutler). Serial electrocardiographs showed the progressive changes of a posterior myocardial infarction, with the development of an intraventricular conduction defect (figure 3).

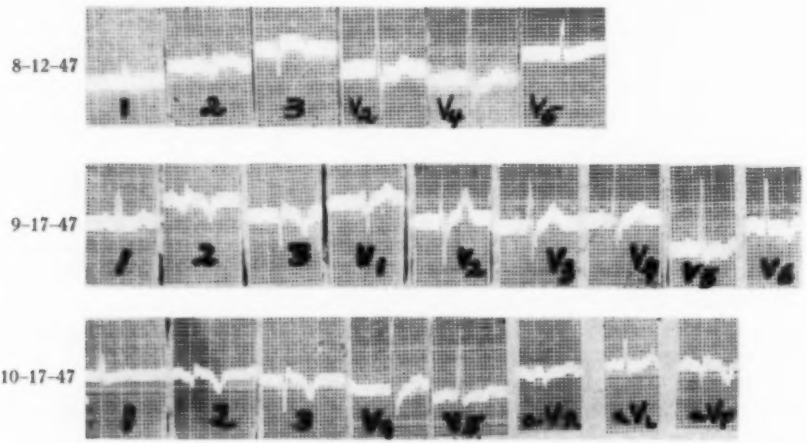

FIG. 3. Case 4.

Atypical Group: This category contained 41 patients with symptoms of cardiovascular insufficiency (though these were not necessarily the patient's major complaints), but with no history of any acute episode which could be interpreted as due to myocardial infarction. This group together with the asymptomatic group exemplifies instances of so-called "silent" infarction. The incidence of the cardiovascular complaints in the patients in the atypical group is presented in table 5. It is apparent that the commonest complaints

were angina pectoris and exertional dyspnea. None of these patients had a history of a severe episode of prolonged chest pain suggestive of infarction.

TABLE V

Incidence of Complaints in the Atypical Group

Angina pectoris	27
Exertional dyspnea	23
Diurnal ankle swelling	7
Atypical angina	7
Paroxysmal nocturnal dyspnea	3
Palpitation	2
Ready fatigability (only symptom)	1

The duration of symptoms varied as follows:

Less than one month	8 patients
One to six months	14 patients
More than six months	19 patients

The briefest duration of symptoms was 10 days and the longest was six years.

Three patients were in obvious congestive heart failure at the time of examination and were unable to work. The others were holding down their jobs with varying regularity depending on the severity of their complaints. The electrocardiographic location of the infarct was anterior (or lateral) in 26 patients, and posterior in 15. Three were still in the "injury stage."

Representative case histories in this group are quoted below:

Case 5. A 27 year old white male for two years had had intermittent retrosternal squeezing pain radiating to both shoulders, associated with cold perspiration, generally developing after walking (especially in cold weather), heavy meals, or coitus, never present at rest, and relieved in a few moments by rest or nitroglycerine. A positive Kahn had been found at an induction examination, and the patient had received weekly anti-luetic treatment for one year. The patient denied any knowledge of primary or secondary lesions. Physical examination was not remarkable. The blood pressure was 112/82. There was no clinical or roentgenologic evidence of luetic aortitis. Sedimentation rate was 15 mm. in an hour (Cutler). The blood Kahn reaction was positive in a titer of 1:4. The spinal fluid Kahn test was negative. Electrocardiographs revealed abnormal Q waves and sharply inverted T waves in Leads II, III, and AV_F, consistent with an old posterior infarct.

Case 6. A 43 year old white male had had, during the previous month, periodic precordial burning pain radiating to the left shoulder and down the inside of the left arm, associated with slight dyspnea, occurring almost daily, precipitated by heavy meals or exertion, relieved immediately by rest. Physical examination was not remarkable except for an incomplete inguinal hernia. The blood pressure was 156/84. Laboratory studies including a chest x-ray and a sedimentation rate were normal. Electrocardiographs are reproduced in figure 4, and show characteristic changes in the healing of a recent anterior infarct.

Case 7. A 53 year old white male, one month prior to examination on completion of his working day, developed nausea, vomiting, and slight dyspnea. Since then he had noted ready fatigability and minimal diurnal ankle swelling. There had never been any chest pain. The patient had been given digitalis during the two weeks prior

to examination. Physical examination revealed a harsh systolic murmur at the apex, and minimal ankle edema. The blood pressure was 110/70. The sedimentation rate was 13 mm. in an hour, and the chest x-ray showed slight enlargement or dilatation of the left ventricle. Other laboratory studies were not remarkable. The electrocardiogram showed changes consistent with recent anterior myocardial infarction,

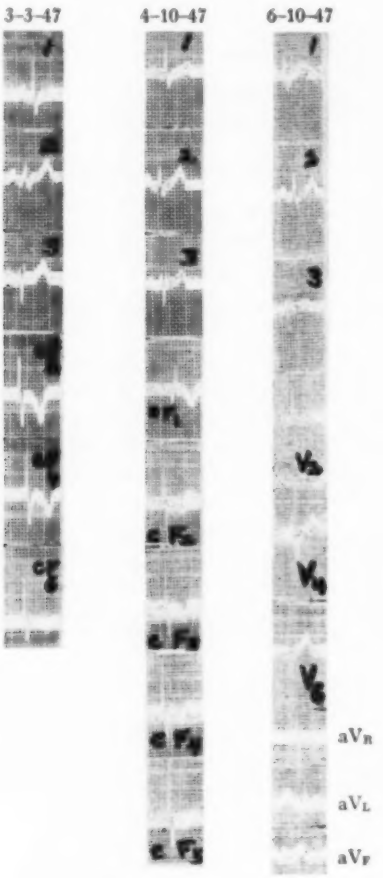

FIG. 4. Case 6.

plus multiple ventricular premature contractions, with runs of bigeminy and pairing (figure 5).

Case 8. A 59 year old white male, beginning two months prior to examination, noted postprandial and exertional angina and dyspnea. He discontinued smoking two weeks prior to examination, whereupon these difficulties promptly subsided. Physical examination yielded no significant abnormalities. The blood pressure was

146/82. The blood Kahn was doubtful positive, but there was no history suggestive of luetic infection. Sedimentation rate, chest x-ray, and other laboratory findings were normal. The electrocardiographs (figure 6) were consistent with a relatively recent anterior infarct. The P–R interval was 0.21 second in the first tracing, but was normal in the subsequent ones.

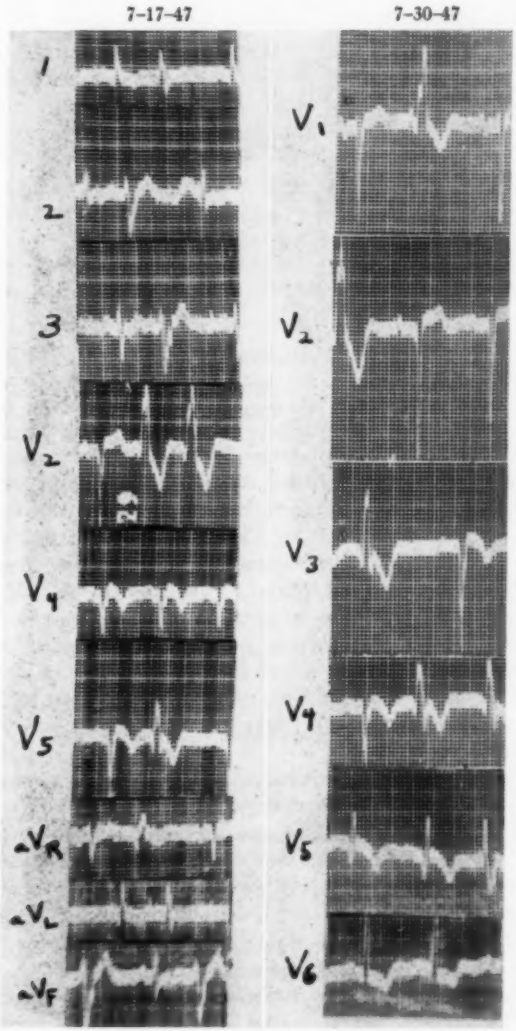

FIG. 5. Case 7.

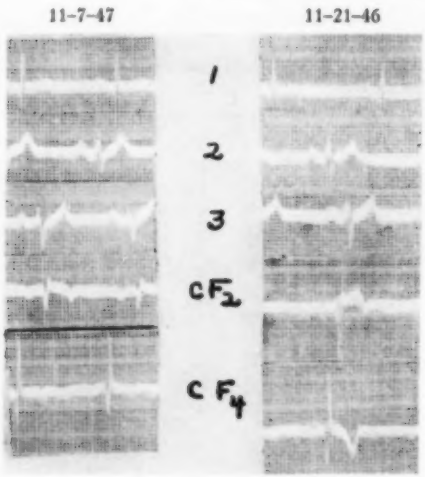

FIG. 6. Case 8.

COMMENT

Any inferences we may draw from the material presented herein must be modified by our realization that the clinical data are based on the patients' histories and are subjective in origin, thus being open to the usual criticism which applies to non-objective data. We feel therefore that statistical inferences are unwarranted. We cannot eliminate failing memories as a source of error in our material, but it is our impression that wilful withholding of information was non-existent, since these patients consulted the clinic for advice for their own benefit. A similar study, for example, performed by the medical departments of the industrial plants where these patients worked would introduce the fear that their employment status might depend on the findings and might therefore lead to the concealment of pertinent information.

This study has served to reëmphasize several points for us, primarily the wide variability of the symptomatology of myocardial infarction. Forty-eight of our 100 patients with electrocardiographic evidence of old or recent infarction did not have the typical history associated with coronary occlusion. In seven patients, there were no cardiac symptoms whatever, and in 41 patients the symptoms consisted primarily of exertional angina and/or dyspnea, or gradual development of mild to severe congestive failure without any history of an acute cardiac episode.

It might be expected that the incidence of painless myocardial infarction in a series of hospitalized patients would be relatively low, since these patients were hospitalized because of their symptoms; similarly reports of consecu-

tively autopsied patients with acute myocardial infarction will have a low incidence of atypical symptoms. The significant thing is that the patients in our atypical group and many even in the typical group were not in sufficient discomfort to stop working.

The functional capacity of patients who have had a myocardial infarct is of great economic importance to themselves and to the community. Levine and Phillips [7] studied the employability of 84 patients who had suffered myocardial infarction at the Kaiser Shipyards. Of 70 patients who survived one year, 52 or 74 per cent were employable. Master and Dack [7b] studied the rehabilitation of patients following coronary occlusion, and found that more than half of their 415 patients returned to full-or part-time work. They concluded that an attack of coronary occlusion in itself is not a sufficient reason for permanent disability. Our experience with the group of patients herein reported tends to corroborate that opinion. In the typical group of 52 patients only three were disabled by angina to the extent that they were unable to work. In the atypical group, three patients were in obvious congestive failure and were unable to work, but the others were working with varying degrees of regularity depending on the severity of their symptoms.

Conclusions

1. One hundred ambulatory patients with electrocardiographic evidence of old or recent myocardial infarcts were studied.

2. Fifty-two patients had typical histories of acute coronary occlusion, though many of these were so diagnosed only in retrospect after electrocardiographic studies.

3. In seven patients myocardial infarction was an incidental electrocardiographic finding. These patients had no cardiac symptoms.

4. Forty-one patients had only mild symptoms suggesting cardiac insufficiency, such as exertional angina and/or dyspnea.

5. Of the whole group only six were totally disabled; the others were able to continue at their jobs even though some had intermittent symptoms.

The material comprising this study was obtained from the files of the Health Institute, Detroit, Michigan.

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THE USE OF SYMPATHETIC NERVE BLOCK IN THE AMBULATORY PATIENT WITH SPECIAL REFERENCE TO ITS USE IN HERPES ZOSTER *

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Owing to the classical work of Leriche of France, and Adson, White, and Smithwick of this country, our present day concepts of the control of certain painful syndromes through the interruption of the sympathetic pathways has been generally accepted. This knowledge has become so well known that sympathetic nerve blocks are now a common office procedure. The scope of this paper is limited to the use of procaine nerve block in the ambulatory patient with special emphasis on the treatment of herpes zoster by this method.

Herpes Zoster

Present evidence supports the opinion that herpes zoster is essentially a posterior poliomyelitis due to the virus of chickenpox. Children exposed to adult patients with herpes zoster may develop chickenpox and adults may develop herpes when exposed to children with varicella. Pathologically, the lesion consists of an acute inflammatory process mainly in the dorsal spinal ganglion accompanied by degeneration in the corresponding sensory nerve, dorsal root and posterior horn cells.[1]

Clinically the patients complain of prodromal hyperesthesia followed by vesicular eruptions corresponding to the involved nerve segment and accompanied by excruciating, burning, tingling, neuritic type of pain. The diagnosis is usually apparent once the typical vesicles appear. The pain is usually so severe that medical relief is sought early.

Numerous and various treatments have been advocated. Among these are diphtheria antitoxin, posterior pituitary extract, prostigmine, gynergen, sodium iodide, cobra venom, and various topical applications together with small and large doses of vitamin B_1. This multiplicity of therapy indicates that the optimum treatment is still being sought.

Our interest in the treatment of herpes zoster by sympathetic nerve block was initiated by the report of A. Street [2] in 1943. He reported excellent results in three cases where he used procaine block. Findley and Patzer [3] reported four cases treated by paravertebral procaine block with instant relief from pain and rapid healing of the lesions. Rosenak [4] in 1938 reported 22 cases treated by procaine block with similar good results.

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Why procaine block of the sympathetic ganglia should relieve the pain and cause drying of the vesicles is not clearly understood. Findley and Patzer [5] advanced the theory that sympathetic ganglion block interrupts a vicious cycle of nerve impulses. Relief of pain and healing of vesicles occurs due to the relief of vasospasm and accompanying hyperemia.

The technic of sympathetic nerve block has been described in detail by numerous authors.[3, 5, 6] The method used in this series consists of treating herpes zoster about the face and neck by procaine block of the stellate ganglion through the anterior approach using 8 c.c. of 1 per cent procaine hydrochloride. Lesions involving the thoracic and lumbar segments were treated by paravertebral block of the sympathetic ganglion, blocking usually one or two segments above and below and including the involved ganglion. In lesions involving the lower extremity, lumbar ganglion Nos. 1 through 4 were injected using 8 c.c. of 1 per cent procaine at each site.

In the past five years we have treated 22 cases of herpes zoster by regional procaine sympathetic ganglion block. The ages of these patients ranged from 30 to 75 years with an average of 49 years. Nine were female and 13 were male. There were three colored patients and 19 white. Twenty patients were seen in the early stages of herpes, an average of five days after onset of pain and three days after eruption of vesicles. Fifteen patients, or 75 per cent, were immediately and completely relieved of pain by one sympathetic block. Five patients, or 25 per cent, required a second block, usually two days after the initial injection, because of some return of pain. In all cases vesicular eruptions began drying promptly and in two to four days remained only as dry crusts.

Two patients were seen four weeks following onset of herpes with post herpetic neuralgia and scarring of the site of healed vesicles. In one patient the procaine block gave temporary relief of pain but four days later a second block was necessary which gave complete and lasting relief. The other patient was seen with severe neuralgia of the facial region. There was very little relief from two stellate ganglion blocks given at 24 hour intervals. Because of severe pain requiring frequent and large doses of narcotics, and the failure of sympathetic blocks to give relief, it was decided to try tetraethyl-ammonium chloride intravenously. Etamon chloride (.4 gm.) was given by vein with prompt lowering of blood pressure and evidence of good autonomic block lasting for one hour. Following this the patient was completely relieved of pain and had required no further narcotics when last seen five days later. Although no definite conclusion can be reached from this one case, we find it of interest and contemplate further investigation.

Case Report: Herpes Zoster

Sympathetic block has not prevented the formation of vesicles not present at the time of block nor will it relieve the pain which accompanies eruption of these new vesicles. The following case illustrates this observation:

A 30 year old white female Graduate Nurse presented herself with a history of burning, tingling pain of 24 hours' duration involving the right groin and buttocks. Examination revealed redness and hyperesthesia of the right groin. Twenty-four hours later typical vesicular lesions appeared accompanied by fairly severe pain. The following day, the pain became so severe that the patient demanded relief. Lumbar paravertebral sympathetic block was done, infiltrating the first through fourth lumbar sympathetic ganglion with 1 per cent procaine. There was immediate relief of pain which lasted several hours, at which time a new group of vesicles appeared lower on the thigh and accompanied by severe pain in this region. There was no return of pain at the site of the original vesicles. The next afternoon lumbar sympathetic block was repeated with complete and permanent relief of all pain. At this time the first set of vesicles was drying rapidly. Following the second block the remaining vesicles dried rapidly and no further discomfort was experienced.

Bell's Palsy

We have had the opportunity of treating seven patients with Bell's palsy by stellate ganglion block. All patients were seen early except one who was observed two weeks after the onset of symptoms. Five cases showed marked improvement with a rapid clearing of the paralysis varying from a few days to two weeks. In these five cases, one sympathetic block was sufficient in three patients, two blocks being required in the remaining two cases. Two patients showed absolutely no improvement despite repeated stellate ganglion block.

Although relief of paralysis was obtained in five of seven cases of Bell's palsy, the mechanism of this relief is unknown. It is possible that stellate ganglion block has its effect through relief of vasospasm and the production of hyperemia, thus reducing edema of the facial nerve.

Intercostal Neuralgia

Only recently we have tried sympathetic block in persistent intercostal neuralgia, in only those cases where no pathological lesion could be found and in patients who had symptoms of several weeks' duration. We have obtained relief of pain in the few cases tried but because of segmental anesthesia it is undecided as to whether the results were due to sympathetic or sensory nerve block.

Summary and Conclusion

The use of sympathetic ganglion block for relief of painful syndromes in the ambulatory patient, especially herpes zoster, has been presented. Twenty-two cases of herpes treated by sympathetic block have been analyzed. The result in all cases has been good with prompt relief of pain and rapid drying of the vesicles. In approximately three-fourths of the patients, only one block was required. Five cases required a second block for lasting relief.

Two cases of post herpetic neuralgia were treated by this method with fair results, one case required tetra-ethyl-ammonium chloride for complete relief.

Seven cases of Bell's palsy were treated by procaine block of the stellate ganglion. Results were good in five cases. Two patients showed no improvement.

The use of sympathetic block in intractable intercostal neuralgia has been tried but results are as yet inconclusive.

Regional sympathetic nerve block is a simple and safe procedure which can usually be performed in the out-patient clinic. Its use in the treatment of certain painful syndromes is advocated and is the procedure of choice in the treatment of herpes zoster.

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NICOTINIC ACID IN THE TREATMENT OF CERTAIN DEPRESSED STATES: A PRELIMINARY REPORT *

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INTRODUCTION

THE increasing scope of psychosomatic medicine has reëmphasized the inter-relationship of psyche and soma in the production of various pathologic disorders.

Alterations in certain physiologic processes are evident in such conditions as schizophrenia, manic depressive reactions, benign depressions, and tension-anxiety states. Among these alterations, changes in body temperature, endocrine functions, biochemical factors, and the circulatory system have been observed. Investigations have suggested that such alterations may prove of etiologic significance in the production of certain of the above mentioned syndromes. These investigations, while highly interesting, have on the whole been inconclusive and not infrequently at variance. These contradictions, although discouraging, may be explained in part by the complexity of the syndromes studied, the variety of methods employed, the difficulty of effecting standardized procedures, and the problems entailed by the patients themselves.

However, despite these difficulties it appears definitely worthwhile to continue to investigate every reasonable possibility of physiologic alterations in various psychiatric disorders. Such investigation does not overlook the psychopathology inherent in the syndrome itself nor does it underestimate the necessity for dynamic psychotherapy. Rather it regards each patient as a psychosomatic challenge requiring an over-all therapeutic approach. If physiologic fluctuations are present and can be treated with some degree of symptomatic relief, psychotherapy may prove not only to be of shorter duration, but of greater and more lasting benefit to the individual.

This preliminary report is limited to (*a*) an investigation of the possibility that cerebral vascular fluctuations occur in certain depressed states, and (*b*) a summary of the rationale for and the use of nicotinic acid in 15 patients who exhibited various depressions and who have been observed over periods ranging from three months to four years.

I. Survey of Previous Reports. A possible relationship between alterations in the circulation of the blood and various psychiatric disorders has been postulated by a number of workers. Nolan Lewis [1, 2] called attention to a tendency towards an aplasia of the cardiovascular system in schizo-

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phrenia. He noted the frequency with which small hearts and aortas were found at necropsy, the intima of the aortas resembling those seen in a younger age group. A similar aplasia was also observed in the cerebral vessels while the capillaries of many viscera were decreased in size.

In surveying a limited number of schizophrenics, Farrel and Vassaf [3] reported an increase in heart size coincident with insulin therapy and clinical improvement. Pathologic anomalies in the capillaries of the nail beds were found to occur more frequently in a group of psychotics than in a group of controls by Schrijver-Hertzberger.[4] Finkelman and Haffron [5] reported, "a low circulating blood volume in patients with dementia praecox," lower than was found in manics, "whose circulating volume approaches normal values." Rosenbaum et al.[6] observed that while the average intracranial blood flow in schizophrenics "did not differ significantly from that in the control group, the values from person to person showed much greater scattering."

In an interesting study of the physical signs of schizophrenia, Klingmann [7] emphasized the cardiovascular aplasia, cyanosis, and hypothermia of the extremities and called attention to spasm of the radial arteries, particularly noted in catatonic schizophrenics and in anxiety schizoid states. This spasm disappeared with clinical improvement. The author suggested that cerebral vasospasm might also be present and of significance in the production of the psychologic symptoms. Jung and Carmichael,[8] on the other hand, felt that the immobility of the stupor case could explain the peripheral vasoconstriction and cyanosis of the extremities. (It has repeatedly been our experience that during the intravenous administration of sodium amytal to patients exhibiting schizophrenic stupor, a disappearance of the cyanosis of the hands occurred during the injection and while the patient was *still immobile,* and that coincident with the return of natural color to the hands, the patient "awakened.")

In 1939 Himwich et al.[9] published an article on the "Biochemical Changes Occurring in the Cerebral Blood during the Insulin Treatment of Schizophrenia." Their study emphasized the diminished use of oxygen by the brain during insulin hypoglycemia. They concluded that "the mental activities like the neurological are dependent on brain metabolism." They called attention to the similar effects produced by anoxia and hypoglycemia. The symptoms of oxygen depletion at high altitudes are described as first, "those of release; excitement, exhilaration and emotional outbursts—later depression, mental and sensory dullness." The cerebral metabolism in 33 patients with depression was studied by Himwich, Cameron et al. in 1945.[10] They reported "no change in the cerebral blood flow" and concluded that "brain metabolism is probably normal in these patients."

Hoskins [11] in his book "The Biology of Schizophrenia," notes that (*a*) the average systolic and diastolic blood pressures were lower in a group of 180 schizophrenics than among a control group of 323 medical students, (*b*) "the schizophrenic subject in the basal state commonly shows a less than nor-

mal frequency of the heart rate." He continues, "we at any rate are convinced that among his other handicaps the schizophrenic patient labors under a considerable tendency to circulatory sluggishness."

The above publications with many others, too numerous to mention here, suggest possible deficiencies in cerebral circulation and oxidation in schizophrenia. Such deficiencies might be explained on (*a*) pathologic alterations in the permeability and metabolism of the brain cells, which render them (partially or completely) unable to utilize the various oxygen and carbohydrate constituents of the blood, and (*b*) a capricious flow of blood through the cerebral vessels, probably on the basis of vasospasm, so that the metabolism of the brain cells becomes secondarily impaired with resulting anoxia.

In the light of our present knowledge it is impossible to say which of *these two* is primary or which is secondary. We would, however, question the conclusion of Himwich et al., quoted above, that their failure to demonstrate changes in the cerebral blood flow in 33 depressed cases indicates that "brain metabolism is probably normal in these patients."

II. Rationale for the Present Study. Although this report is primarily concerned with depressed states and not with schizophrenia, we have surveyed the literature on the latter in reference to circulatory alterations, not only because more material is available regarding schizophrenia, but because depressive reactions and schizophrenia exhibit various similarities. Thus both schizophrenic and depressive reactions manifest resemblance in their regressive patterns, apathy, retardation, blocking, withdrawal and flattened affect. That the resemblance is a surface one and hence superficial is clear, since the archaic immature "underlay" of schizophrenia plus its bizarre and grotesque thought processes are lacking in the depressed, non-schizophrenic patient. Despite complex dynamic variations, there are, however, the possibilities that (1) schizophrenia represents a "malignant" psychosomatic syndrome, whereas depressed states may be regarded as "benign," less complicated reactions, and that (2) both may proceed from similar biologic disturbances.

It is also quite possible that hereditary predisposition to either schizophrenia or depression is associated with a defective brain metabolism and/or circulatory impairment which represent a familial "weakness." Viewed in this light, schizophrenia might be compared to malignant hypertension, depressive reactions to benign hypertension, the former often basically irreversible, the latter reversible.

In addition to these considerations, there are certain pharmacological similarities which appear pertinent. Various investigators [12, 13, 14] have reported that such drugs as epinephrine, amphetamine, and ephedrine not only fail to produce improvement in schizophrenia, but occasionally appear to increase the symptoms. It has been our experience that the same holds true in the more serious type of depression, though mild, so-called "situational," depressions may of course be ameliorated or relieved by such agents.

On the other hand, *favorable* results in the treatment of schizophrenia

have been reported from the use of sodium amytal, alcohol, cocaine, carbon dioxide inhalations and shock therapy. Many of these have also proved beneficial in severe depressions.

It is of interest to recall that despite their varying properties and actions, the *pharmacologic agents which have proved negligible in the treatment of schizophrenia possess in common certain vasoconstricting effects,* while *those pharmacologic agents which tend to improve the condition have certain vasodilating effects.*

With these thoughts in mind, we undertook in the fall of 1944 a search for an effective vasodilator in the treatment of depressive reactions. Much valuable and greatly appreciated encouragement and advice were obtained from Professors Arthur Tatum and O. S. Orth of the Department of Pharmacology at the University of Wisconsin, and upon the suggestion of the latter, nicotinic acid was selected for therapeutic trial. Its selection was determined on the basis of (*a*) its known value as a potent vasodilator, (*b*) its low toxicity, and (*c*) the ease of administration. Additional impetus for the use of nicotinic acid was found in the reports of Cleckley, Sydenstricker and Geislin [15] and Sydenstricker and Cleckley.[16] These papers deal respectively with the use of nicotinic acid in "the treatment of atypical psychotic states associated with malnutrition" and in "stupor, lethargy and various other psychiatric disorders."

Commenting upon some of the favorable results which they obtained, Sydenstricker and Cleckley [17] state, "One is—led to the conclusion that in the illness of the patients here discussed, factors other than dietary disturbances played important rôles—factors yet undetermined and perhaps unsuspected may also influence the failure of the neurones to receive and utilize an adequate supply of vitamins." In discussion, Airing [18] called attention to the effects of nicotinic acid on the cerebral circulation which produce "a marked increase in cerebral blood flow." Cleckley concluded [19] that "it is of course possible, perhaps probable in some cases, that the beneficial effect we observed after the administration of nicotinic acid was the result of dilatation rather than the correction of an acute deficiency state."

III. Summary of the History and Findings on the Patients Treated with Nicotinic Acid.

A. *The selection of patients.* Between February, 1945, and July, 1948, we administered nicotinic acid as a pharmacologic adjunct to psychotherapy to 29 patients manifesting various types of depressions. However, a careful analysis of the records indicates that in 14 cases the results were too inconclusive to permit consideration here. This may be attributed to (1) failure on the part of a number of patients to follow through with their treatment, (2) abide by the recommended dosages, (3) report at regular intervals, (4) withdrawal from the University, and (5) various personality complications coupled with so high a degree of suggestibility that objective evaluation has been impossible. The 15 cases selected from the original 29 have been under observation for periods ranging from three months to four years. All

of this group were students enrolled in the University of Wisconsin. Nine were males and six females. Their ages ranged from 18 to 46. Eleven of these received nicotinic acid for more than one period of trial. All members of this group have been coöperative in following out the program outlined to them.

Inasmuch as this is a preliminary report, the data obtained and the results observed are presented here in a summary form.

B. *The chief complaint.* In each case the chief complaint was "depression." In five patients the depression was evaluated by the therapist as "benign" with no demonstrable underlying psychopathology of a serious nature. In five patients the depression was viewed as a phase in a manic depressive reaction. In four patients deep-seated schizophrenic patterns were present. In one patient the depression was initially overlaid with a toxic psychosis.

Comment: Of the four patients who exhibited a schizophrenic "underlay" one had been previously seen by us in 1944 during an acute psychotic episode. For this he received elsewhere a prolonged course of electric shock treatment. A satisfactory remission was obtained so that the patient was able to resume his university work. His subsequent course has been fairly satisfactory with the exception of periodic depressions. The second patient in this group was rapidly developing a schizophrenic psychosis when first seen and treated with nicotinic acid. The third and fourth patients represented latent or ambulatory schizophrenic reactions without, at the time, psychosis.

The patient with the toxic psychosis was a 28 year old female, a graduate nurse enrolled for part-time work in the University. A severe depression of three weeks' duration had led to self administration over a five day period of 11 *grains* of ephedrine and 8 *grains* of thyroid extract. When first seen the patient exhibited the usual signs of a toxic reaction including aural hallucinations, extreme agitation, and elevated blood pressure.

C. *Discussion of the depression.* In all of the group, excepting only the last case (the toxic psychosis), the patients' initial description of the depression included the following statements, "I have lost interest in everything—I have no ambition any more—everything seems futile—I feel frustrated and lonely—I can't remember or concentrate—I am *all slowed up.*" Nine patients had found it impossible to drive themselves to class. Three admitted staying in their rooms in order to "avoid seeing anyone." Three had experienced feelings of unreality and dissociation and six entertained ideas of suicide.

In view of the previous discussion concerning the non-effectiveness of ephedrine in schizophrenia, it was of interest that even before the patient with the toxic psychosis experienced the effects of overdosage, she had found no relief for her depressed state, but maintained that she kept on taking more ephedrine "in hopes of feeling better."

Clinically, the 15 patients exhibited varying degrees of retardation, blocking, and flatness of affect. In seven cases there was hypothermia and

subcyanosis of the hands and feet. The majority complained of anorexia although two had experienced an increased desire for food, particularly carbohydrates. Constipation concurrent with the depression was present in eight. Three had insomnia, while 12 stated that during the depression they slept for longer periods of time.

D. *Past history.*

1. Familial histories of similar depressions were present in four of the 15 patients studied.
2. Previous depressions with a duration of two days to four months had been experienced by all 15.
3. Situational conflicts, most commonly arising from sexual, home, or university maladjustments, were present in 11 cases and were considered of etiologic significance in the production of the depression.
4. Seasonal tendencies were found in seven cases; three experienced depressions in the summer, two in the winter and two in the spring and fall.

E. The period of clinical observation before, during and after the use of nicotinic acid is illustrated on the following chart.

During these three periods, that is before, during, and after the use of nicotinic acid, psychotherapeutic conferences were held with all patients.

F. *Technics for administration of nicotinic acid.*

1. Preliminary. In an endeavor to establish as much uniformity as possible, all of the patients were (*a*) given a similar brief explanation covering our reasons for selecting nicotinic acid as an adjunct to psychotherapy. In this brief explanation they were told that they might or might not be helped by this medication. (*b*) They were given written schedules for oral

	Before			During			After		
	Years	Months	Weeks	Years	Months	Weeks	Years	Months	Weeks
1	3	2			3			5	
2		3		1*			—	—	—
3			1			5*			2
4	1				2			6	
5		1				3			1
6	—	—	—		6*		—	—	—
7	—	—	—	1*	5*		—	—	—
8			2			4 da.		2	2½
9		6			9*		—	—	—
10		5				5 da.	—	—	—
11		6		1*	4*		—	—	—
12		3			2*		—	—	—
13	—	—	—		2			3	
14	—	—	—			3		2	
15	3	8			4			4	

* During this period nicotinic acid was used intermittently, that is on more than one occasion.

dosage. (*c*) They were requested to return for biweekly or weekly check-ups, and (*d*) were asked to keep a separate chart of their dosages and the effects noted. Several patients with depressive reactions not included in this group were deemed unsuitable for nicotinic acid therapy because of a history of (*a*) migraine, (*b*) peptic or duodenal ulcers, and (*c*) ulcerative colitis.

2. Intravenous administration. Nicotinic acid was *initially* administered by the intravenous route to 10 patients. In nine instances this was immediately followed by oral administration according to a schedule suggested by Dr. Orth. The tenth case received no oral therapy until three months after the initial intravenous injection. The patients who were to receive intravenous therapy were admitted to the Student Infirmary and put to bed. A .05 per cent solution of nicotinic acid in sterile physiologic saline solution was injected intravenously at the rate of 20 to 30 drops per minute for a total dosage of 300 to 400 mg. of nicotinic acid. The amount used was determined in each case by the degree of flushing and warmth which ensued as well as any evidence of hypersensitivity or untoward reactions to the drug. (Incidentally, no hypersensitivity or untoward reactions were manifested by any of this group.) The time required for the administration varied from three to six hours. At the conclusion of this the patient was discharged from the hospital and was given a prescription for two hundred 50 mg. tablets of nicotinic acid together with a typed schedule of instructions for its oral use, the first dosage to be taken preceding the next meal.

3. Oral administration. Five patients received nicotinic acid initially by mouth and were so continued, no intravenous therapy being employed at any time. The schedule for oral administration was the same as with those who had received the drug intravenously.

The schedule for oral administration was as follows: "(*a*) For the first two days, three 50 mg. tablets are to be taken at 15-minute intervals preceding each meal. Example—breakfast hour 8 a.m., first tablet at 7:15, the second tablet at 7:30, the third tablet at 7:45. (*b*) If no untoward reaction, such as headache or nausea, occurs, the dosage is to be increased on the third and fourth days as follows: four 50 mg. tablets are to be taken before each meal, according to the 15-minute schedule, the additional tablet being added to the first dosage; example 100 mg. — 50 mg. — 50 mg. (*c*) On the fifth and sixth days five 50 mg. tablets are to be taken before each meal, the additional tablets being added to the first and second dosages; example 100 mg. — 100 mg. — 50 mg. (*d*) On the seventh and eighth days six 50 mg. tablets are to be taken at the 15-minute schedule before each meal, two tablets being taken together; example 100 mg. — 100 mg. — 100 mg." Thus by the eighth day the patient was receiving a total of 900 mg. a day. In five instances it was necessary to continue to increase the dosage in the fashion outlined, in one instance going as high as 2500 mg. The patient was maintained on the maximum dosage for a period of one week to 10 days at which time the dosage was decreased in the same order as it had been increased.

The average duration for the administration of nicotinic acid thus varied from periods of two to six weeks.

G. *Physiological effects.* Fourteen patients noted flushing to a greater or lesser degree, particularly marked in the face, neck and arms. Five patients complained of moderate headache, three of nausea, one of occasional emesis, two of pruritus, two (male patients) noted increased hirsutism, and 11 stated that they experienced a rather disagreeable taste and smell after taking the drug.

H. *Summary of the effects noted.* Fourteen out of the 15 patients exhibited subjective and objective improvement following the use of nicotinic acid in conjunction with psychotherapy. This improvement was characterized in all instances by the following common denominators: (1) the improvement followed the combined intravenous and oral administrations within a period of 24 to 48 hours; (2) it followed the oral administration alone within a three to five day period; (3) the improvement took place rapidly, that is a change in affect combined with a sense of well being was noted by the patient within a period of a few hours.

The following comments on the nature of the improvement are taken verbatim from remarks volunteered by the patients. Case 1 (an ambulatory schizophrenic who had experienced a previous psychotic episode), "I have a sense of well being. I find I can think more rapidly and clearly. I don't block as much. My sleeping is improved. Life seems more worth living." (This patient had failed in a master's examination three months previously due to his slowness in thinking, blocking, and inability to express himself. Following his improvement on nicotinic acid he repeated the examination and passed creditably.) Case 2 (the toxic psychosis), "I feel fine; I am no longer bothered by the voices and I am not depressed." Case 3 (manic depressive reaction), "I began to feel as though life was worth it. It started quickly; I feel energetic and like going places." Case 4 (benign depression), "These pills are O.K. My point of view is a lot better. I am still slowed up, but I am not depressed." Case 5 (benign depression), "I began to feel better and more loosened up. I found myself talking to the kids in the next room. Soon after that I felt like going places and I went to a student meeting. I haven't enjoyed seeing people for several weeks." Case 6 (benign depression), "Now I can begin to understand many of the things which we have been talking about. I think I understand them better because I am no longer depressed. I can think more clearly." The comments of the other patients were essentially of the same nature. In essence they stressed a lifting or lightening of the depression, improvement in the speed of thinking, increase in and desire for social activity, and a return of work interest.

In the 14 cases who improved, no relapses were exhibited while they were taking nicotinic acid. In 11 instances it was necessary to repeat the procedure at a later date when another depression became evident. In each of these cases *an improvement identical to the first* was obtained on repeating the medication.

The one case which entirely failed to respond, and whose symptoms in fact were made worse, was a 45 year old female who was rapidly developing a schizophrenic psychosis when first seen. With the use of intravenous nicotinic acid she became extremely paranoid, insisting that voices were being introduced into her with the drug.

SUMMARY

A. The rationale for the use of nicotinic acid in certain depressed states is discussed.

B. The observations and results of its use in 15 patients exhibiting various forms of depressions are recorded.

C. While no conclusions can be drawn on the beneficial effects observed in so small a group, the results elicited were of sufficient uniformity to suggest the desirability for further study.

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ELECTROCARDIOGRAPHIC OBSERVATIONS DURING A POLIOMYELITIS EPIDEMIC *

By Henry Alexander Bradford, M.D., F.A.C.P., and Leighton L. Anderson, M.D., *Denver, Colorado*

Myocarditis,[1, 2] although infrequent, has been found in several virus diseases. In 1942, Saphir and Wile [3] described inflammatory changes in the hearts of six patients, from a series of seven, dying of poliomyelitis. The hearts of this series of patients were described grossly as "slightly dilated but not hypertrophied . . . the myocardium was slightly flabby, usually grayish red." Interesting microscopic findings were noted. The perivascular spaces were infiltrated with lymphocytes and neutrophiles in variable numbers—monocytes were present in lesser degree. In half of the cases where the myocardial changes were more severe, there were additional histological features; the lymphocytic infiltration was more diffuse, and in several locations near the endocardium, small foci of lymphocytes were interspersed among extravasated red blood cells; also, in some subendocardial areas the muscle fibers appeared to be swollen and to have lost their striations. Saphir and Wile could offer little correlation between clinical features and the findings of myocarditis. It is of some interest, however, that, in three patients who died suddenly, the evidence of myocarditis was more striking.

Other descriptions of effects upon the heart during poliomyelitis were offered by Peale and Lucchesi [4] in 1943, and by Gefter, et al.[5] in 1947.

A group of workers at the Philadelphia Hospital for Contagious Diseases studied the hearts in 467 cases of poliomyelitis admitted over a three-year period. They observed several clinical features, such as systolic murmurs and disproportionate sinus tachycardia, but were unable to attach much significance to these observations. Electrocardiograms were obtained in 226 non-fatal cases, but not in any of the 11 fatal cases. As might be expected, the majority of the electrocardiographic abnormalities were in patients having the most severe involvement by the disease.

A study of the time-incidence of electrocardiographic abnormalities in the course of the disease suggested that such abnormalities (1) *occurred early in the disease;* (2) *did not increase with the continuance of the disease;* (3) *persisted for at least several weeks.* Among the positive electrocardiographic findings, in order of frequency were: sinus tachycardia (rate above 140), T-wave abnormalities, unexplained left axis deviation, PR prolongation, high-peaked P-waves, significant right axis deviation, displacement of the RST segment, extrasystoles, and slurring of the QRS complexes. Patho-

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From the Department of Medicine, University of Colorado Medical Center, Denver, Colorado.

logical study of six autopsied cases revealed some type of significant finding in all but one heart, apparently both in the gross and microscopic. It is of interest to note that, in three cases, dilatation of the right heart was described. Two cases exhibited the histological features of perivascular and interstitial cellular infiltration as mentioned previously, described by Saphir and Wile.

During the epidemic of poliomyelitis of 1946, a very large number of cases was admitted to the Colorado General Hospital within a six-week period. It had been planned to make serial electrocardiographic studies of all cases. As the surge of poliomyelitis admissions rapidly mounted, it became feasible to obtain only an electrocardiogram as early as possible, and to obtain serial tracings when there was any question of significant findings.

Tracings were taken in a considerable number of respirator cases, and, in fact, were taken in all such cases unless, because of technical difficulties or the critical condition of the patient, this was not possible.

In the latter part of the epidemic some cases were transferred from other localities, and, hence, electrocardiograms of these patients were obtained in relatively later phases of the disease. This group of cases, in which electrocardiograms were obtained later than two months after onset, is not considered in this report, as there is evidence that the electrocardiographic abnormalities may disappear in two months or less.

Results

There were 20 cases in which definite electrocardiographic changes were observed in the course of the disease. No complicating factors, such as previous heart disease or drug administration, were present in these cases. Several additional cases with minor electrocardiographic changes were observed in a group of 15 patients in whom the initial electrocardiogram was obtained later than two months after onset. These cases were not considered as adequately followed and were excluded. Because of the known variations in the electrocardiogram pattern in children,[6, 7] there are no children with T-wave or QRS changes included. Very minor T-wave and QRS changes, as well as temporary fluctuations of the electrocardiogram pattern, were also disregarded.

A. *Sinus Tachycardia.* A total of 12 cases showed sinus tachycardia with a rate exceeding 140, but, of these, eight were children three and one-half years of age, or younger, and their electrocardiograms revealed no other abnormality.

The significance of the effect upon the heart rate in children of this age group is doubtful, and these electrocardiograms were not considered in the group of 20 showing definite changes.

The other four cases with sinus tachycardia were in older patients who also showed alterations in the electrocardiogram pattern and are included in the 20 abnormal cases.

B. *Electrocardiograms Showing T-wave Changes* 16

(a) Principal changes in CF leads 4
(b) Principal changes in limb leads 7
(c) Significant changes in both chest and limb leads 5

C. *Electrocardiograms Showing Pattern of Right Ventricular Strain* 2
D. *Electrocardiograms Revealing Significant Conduction Disturbances* 2

E. 135 cases with normal electrocardiograms were observed within two months after onset of the disease. The electrocardiograms of several patients were considered normal even though there were fluctuating variations of pattern of T-waves.

Of the total of 155 cases with electrocardiograms taken initially within two months, there were 41 cases with bulbospinal involvement. Seven (or 17 per cent) of these cases showed abnormal electrocardiograms.

There were nine cases with bulbar involvement. Of these, two (or 22.2 per cent) had abnormal electrocardiograms.

There were 105 cases with spinal involvement. Of these, 11 or (10.5 per cent) showed abnormal electrocardiograms.

Of the two patients whose electrocardiograms showed right ventricular strain, both had bulbospinal polio of severe grade and one succumbed. It may be significant to note that these two patients (aged 9 and 27) appeared to have marked pulmonary edema.

There were two patients in whom the electrocardiograms revealed a *slight A. V. conduction defect.* Spinal involvement of the disease was present in each. One of these patients was three years of age and the other 16 years of age.

Four instances of significant T-wave alteration in the limb leads were recorded. Three of the patients of this group had spinal involvement, and one had bulbospinal involvement. These patients were 14 years of age or older.

Seven cases revealed the principal T-wave changes in the chest leads. None of these cases with this electrocardiogram pattern change had bulbospinal involvement; five cases had spinal involvement; two cases, bulbar involvement. One patient was 13 years old and the remainder were adults.

Five patients showed significant T-wave variations in both limb leads and chest leads. Of these five cases, four had bulbospinal involvement and one had spinal involvement. All five of these patients were adults.

From an electrocardiographic standpoint there were relatively few cases which revealed changes in the QRS pattern which apparently were associated with the disease. Eight individuals showed QRS pattern changes but all of these had other electrocardiographic variations and were considered in the previous data. Seven patients demonstrated changes in QRS indicating varying influence of the disease on the right ventricle. All patients of this

group were adults except one boy, age nine. Two cases had pulmonary edema and showed the pattern of right ventricular strain. Two additional cases had to be placed in a respirator but did not clinically appear to have serious embarrassment of respiratory function or pulmonary edema. In the group having right axis deviation without strain, fluoroscopic study did not demonstrate a significant shift of the mediastinum adequate to explain this electrocardiographic pattern. All seven patients with right axis deviation had some degree of diaphragm weakness.

One electrocardiogram showed a slight increase in degree of mild left axis deviation. This patient had a spinal type of involvement with paralysis of all four extremities. Hypertension was not observed in this case.

Discussion of Electrocardiographic Abnormalities

Right Ventricular Strain. Two cases of poliomyelitis were observed which displayed a definite electrocardiographic pattern of right ventricular strain. From a clinical standpoint both of these patients were extremely ill with bulbospinal involvement. In contrast to the other bulbospinal cases, the bulbar features developed rapidly and were of severe degree. One case was placed in a respirator and administered oxygen by catheter, and the other was given oxygen by tent; both had pulmonary edema and required frequent tracheal aspiration. We felt that the initial factors precipitating right heart strain might well be the following: paralysis of respiratory movements, anoxic effects upon the myocardium, mechanical pulmonary tree obstruction with thick mucus and possibly toxemia. In passing, we might add that the technical difficulties of obtaining tracings on our respirator cases were so great, that we were unable to follow more of the severely ill patients with bulbar involvement.

Our limited knowledge as to the effects of poliomyelitis as well as other acute infectious diseases upon the physiochemistry of the myocardium precludes any definite explanation of the T-wave changes and AV conduction variations seen in this group of patients. It is well known, however, that such conditions as rheumatic fever, diphtheria, pneumonia, typhoid fever, typhus fever, influenza, periarteritis nodosa, and Malta fever may be associated with T-wave changes, S–T segment shifts, and AV conduction variations. Apparently it is the toxic effect of the disease process upon the myocardium that may produce this type of electrocardiographic change.

Fatal Cases With Poliomyelitis. There were 24 fatal cases of poliomyelitis in the group of 303 observed at the Colorado General Hospital. Electrocardiographic records were obtained on only five of the fatal cases. Four of the fatal cases showed significant electrocardiographic changes. In one of these cases a right ventricular strain pattern was noted, in the other two cases T-wave changes were found. Another fatal case had a normal electrocardiogram early in his disease. A fourth fatality occurring 15 months after onset showed T-wave changes in the chest leads and left axis deviation.

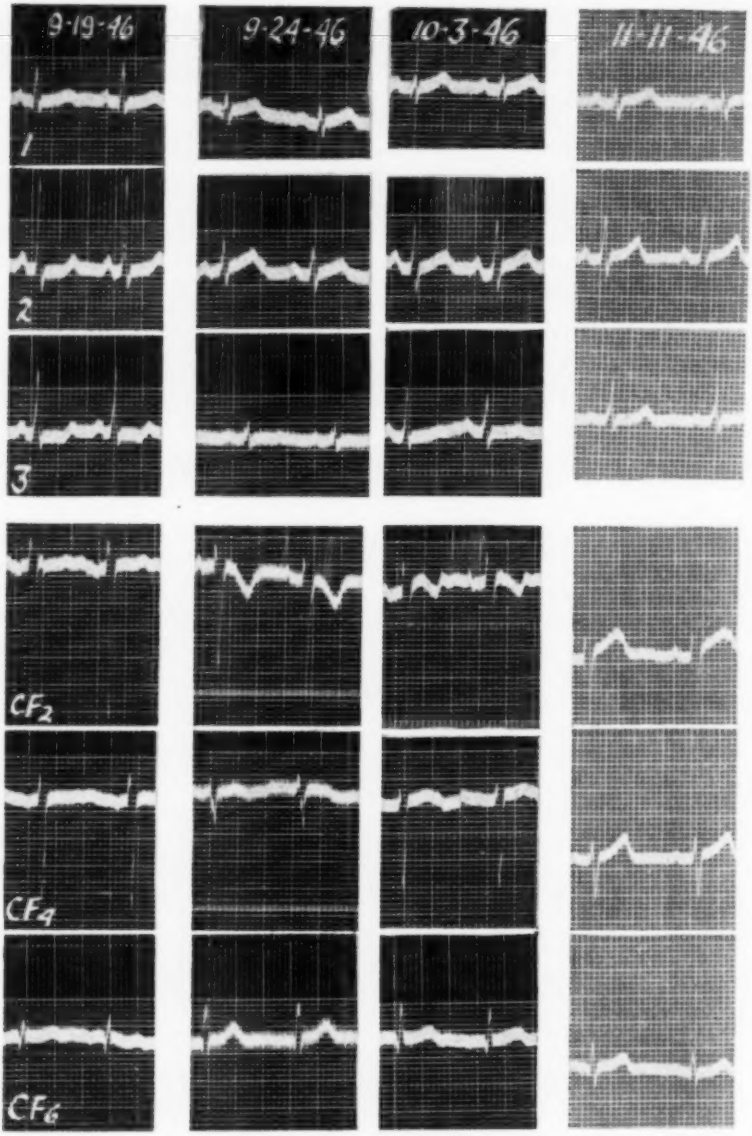

FIG. 1. (*Case 1.*) An initial electrocardiogram eight days after onset revealed low diphasic T-waves in the chest leads; serial electrocardiograms showed a transient increase in the negative phase of the T-waves in CF_2 and CF_4 with an eventual return to a normal form approximately two months after onset.

Pathological Study. In the 24 fatal cases of poliomyelitis, pathological findings in the heart were meager. It should be noted that only the routine sections were reviewed and possibly, if further serial sections were made, the incidence of positive findings would increase. The importance of obtaining numerous sections and studying all carefully to be certain of not missing evidence of myocarditis is emphasized by Gore and Saphir.[8] Of the 24 fatal cases three hearts showed varying amounts of cellular infiltration, chiefly lymphocytes with occasional polymorphonuclear cells and monocytes. The one fatal case with a normal electrocardiogram did, at autopsy, show a slight amount of both perivascular and more diffuse cellular infiltration.

Case 1. A female patient, age 28, was admitted to the Colorado General Hospital on September 18, 1946 with the complaint of flu-like symptoms beginning September 11 and followed by nausea, vomiting, and then generalized weakness. She was near term pregnancy. She became progressively worse with increasing paralysis and respiratory difficulty until it was necessary to place her in a respirator on September 23. About 12 hours later, after a short labor, there was spontaneous delivery of a normal term, male infant, without complication. She did not require the respirator after delivery though oxygen was necessary intermittently for several days. She was fluoroscoped on October 15, 1946 and it was evident that the right diaphragm was paralyzed, with weakness of the left. There was, during the next several months, gradual improvement but with a permanent residual of considerable paralysis of the lower extremities.

This, then, was a patient with acute severe spinal poliomyelitis who recovered except for residual paralysis of the lower extremities, and who had changes in the T-wave pattern in the chest leads of electrocardiograms taken during the course of her disease (figure 1).

Case 2. A male child, age nine years, was admitted to the Colorado General Hospital on September 4, 1946. His illness had begun with fever on September 1, followed by stiffness of the neck and difficulty in swallowing. On admission, in addition to severe spasm of neck, back, and hamstring muscles, there was a slight, left, facial paralysis and blurring of vision. Following admission, the course was of fulminating character. He became comatose with fever to 106° F. rectally, and intermittent tachycardia of 160–180. He remained in critical condition for several days. There was evidence of pulmonary edema with probable cardiac failure. He required frequent tracheal aspiration and continuous oxygen, but was not in a respirator. He was given digitalis intravenously in an attempt to control the bouts of tachycardia, but he was not fully digitalized nor maintained on digitalis. After about a week of nearly a hopeless condition, improvement began and he recovered with little or no residual.

This then, was a case of acute encephalo-bulbospinal poliomyelitis that was moribund for several days, but recovered with little or no residual, and that had an electrocardiographic pattern of right ventricular strain during the acute phase of the disease (figure 2).

Case 3. A male child, age three years, was admitted to Colorado General Hospital on September 22, 1946, with acute poliomyelitis, spinal type, involving the lower extremities, particularly the right. The onset of the disease was on September 17. He was not toxic and had only low grade fever on admission. He did not appear to have severe involvement. He showed gradual, slow improvement and was discharged on October 23, 1946. On December 3 of the same year there was only slight residual weakness of the right lower extremity.

This, then, was a case of acute poliomyelitis, spinal type, which showed only

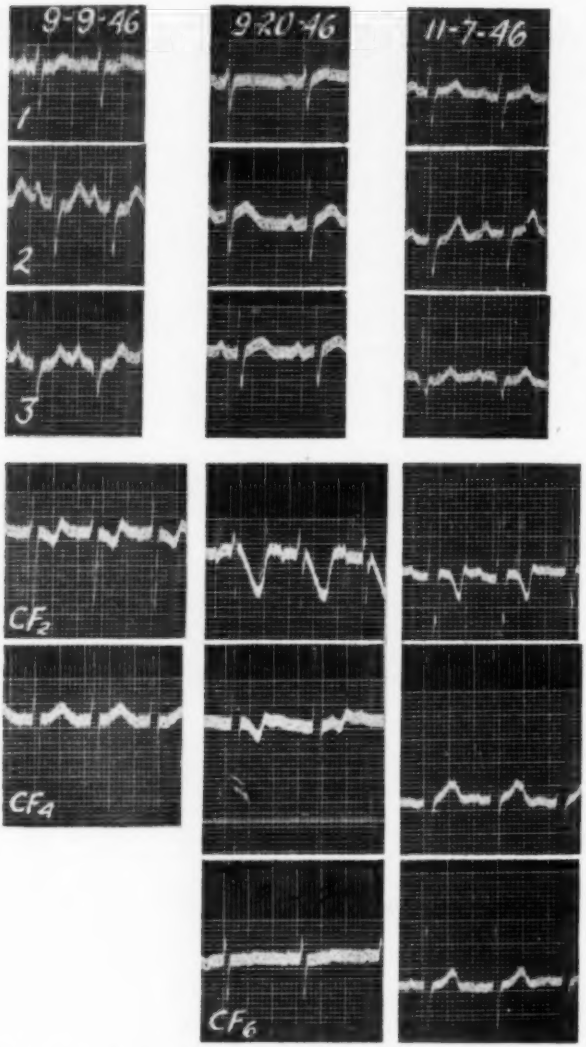

FIG. 2. (*Case 2.*) An electrocardiogram of D. W., aged 9 years, five days after onset, while the patient was apparently moribund with disturbance of the respiratory center and pulmonary edema revealed evidence of right ventricular strain. He was later given intravenous digitalis and oxygen by mask owing to the features indicating right heart strain and also because of the clinical recognition of intermittent tachycardia.

An electrocardiogram on September 20, 1946 about seven days after discontinuance of digitalis showed no evidence of right ventricular strain in the limb leads but did show abnormalities of the T-waves of the chest leads which may have been due to residual digitalis effect. A later electrocardiogram on November 7, 1946 showed right axis deviation but no evidence of strain.

mild, to moderate, initial involvement and, three months later, had only a slight residual weakness of the right lower extremity; but had a prolongation of the PR conduction time on an electrocardiogram taken during the acute phase which improved during convalescence (figure 3).

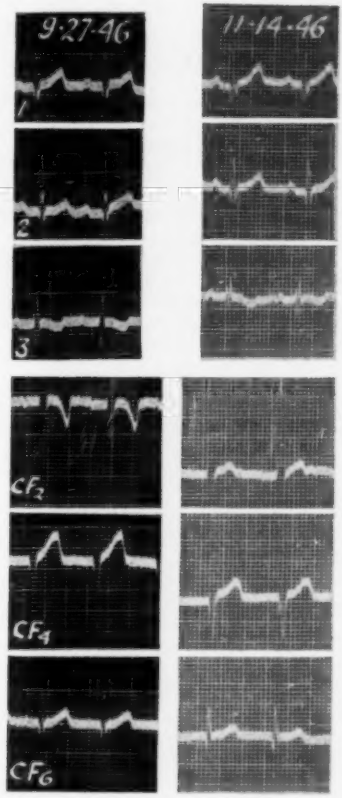

FIG. 3. (*Case 3.*) This electrocardiogram reveals a rate of approximately 100 on September 27, 1946. The PR interval on this date was 0.19 second. Another electrocardiogram on November 14, 1946 in the same case shows a PR interval of 0.15 second. The electrocardiograms, in addition to the changes in conduction time show slight differences in the form and direction of the T-waves in the respective chest leads, but these were held to be of questionable significance.

CONCLUSIONS

1. Electrocardiographic studies were made in a little over half of 303 cases of poliomyelitis during a fulminating outbreak of the disease in Colorado in 1946.

2. Significant electrocardiographic changes were found in about 12 per cent of 155 adequately followed cases. The changes consisted of high grade sinus tachycardia, T-wave alterations, AV conduction variations, and the occurrence of right ventricular strain.

3. Three of four fatal cases displayed positive changes in the electrocardiograms.

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THE EFFECT OF ENDOGENOUS INSULIN ON GASTRIC FUNCTION: A CLINICAL STUDY*

By William D. Poe, M.D., *Roanoke, Virginia*

It has been demonstrated that insulin administration, by reducing the blood sugar level, stimulates the vagal center which results in increased secretory activity in the stomach.[1] It has been proved that the injection of insulin into dogs with gastric pouches will increase the motor and secretory activity of the stomach if only a few vagal fibers are unsevered.[2]

Based on these data, a clinical test has been devised to determine whether vagal activity remains following vagotomy in the treatment of peptic ulcer. If there is increased secretory activity of the stomach following insulin injection in a vagotomized patient, it is concluded that the vagi were incompletely interrupted.[3] In these tests a blood sugar of 50 milligrams per cent is taken as the liminal level at which increased gastric activity will be manifest in all incompletely vagotomized patients.[4]

In view of the above experimental and clinical experiences, it seems worthwhile to correlate gastrointestinal symptoms, and gastric function, secretory and motor, with blood sugar levels in patients with hyperinsulinism. Accordingly, 50 case records, selected at random, of patients whose blood sugar levels were less than 80 milligrams per cent at some time during a six-hour glucose tolerance test were carefully studied with reference to symptoms, gastric analyses and roentgenologic examinations. None of the patients had other significant clinical findings. The patients had an average age of 37.1 years and ranged between 21 and 74 years. There were 32 females and 18 males.

Method of Study

From the case histories an appraisal of symptoms was made. Symptoms were considered as "major" if they were among those which were responsible for the patient coming for consultation. If gastrointestinal symptoms were elicited only on the system review they were considered as "minor."

The determinations of blood reducing substances were made by the method of Folin and Wu. A fasting specimen was drawn, 1.5 grams of glucose per kilogram of body weight, up to 100 grams, were given by mouth. The determinations were made at hourly intervals for six hours. All determinations were made within an hour after the blood samples had been drawn. All glucose tolerance tests were begun after an overnight fast. None of the patients was given a preparatory diet prior to the test.

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From the Seale Harris Clinic, Birmingham, Alabama.

Gastric analyses were made after an overnight fast and patients were not allowed to drink any fluid, smoke, or chew gum previous to the test. A fasting specimen of the stomach contents was obtained, 20 c.c. of 7 per cent alcohol were introduced into the stomach and another sample was obtained 15 minutes later. The specimens were titrated with 0.1 N sodium hydroxide.

The roentgenologic examinations were made by three different experienced observers, a fact which would, naturally, cause some discrepancy in interpretation. The discrepancy due to the human element was minimized by the fact that notes were made on each chart concerning the gastric tone, peristaltic activity, and the state of the duodenal cap immediately after the examination. The examinations were made before this study was prepared. Thus, the judgment of the examiners was not colored by the idea that the data would be used in a study of this kind. The examinations were made after an overnight fast.

In this study the gastric tone and peristaltic activity, and the state of the duodenal cap are taken as criteria for judging gastric motor activity.

Results

By the nature of the study, results are difficult to evaluate since no exact controls could be set up. The difficulty can be appreciated if one considers that one can have similar findings without hyperinsulinism and vice versa. Accordingly, conclusions will be reached from very strong impressions based on the study, since incontrovertible proof depends on exact controls.

It has been observed that some patients who customarily eat breakfast become quite nervous and/or have rather marked hunger sensations if deprived of this morning meal. We have gained the impression that symptoms of fasting are much more marked in patients with hyperinsulinism, and are like those that may occur spontaneously.

It is true that all the studies were not made at the exact time that the blood sugars were known to be diminished below normal, but they were made at such a time that a patient with hyperinsulinism could be expected to have a low blood sugar, i.e. the fasting state, usually in the mid or late morning or early in the afternoon.

Symptomatology: The results of the study of gastrointestinal symptoms in 50 random patients who had hyperinsulinism are summarized in table 1. It will be observed that "minor" symptoms were not counted in patients who had "major" symptoms.

Table 1

Gastrointestinal Symptoms in 50 Patients with Hyperinsulinism

	Number of Patients	Per Cent of Patients
Major symptoms	31	62
Minor symptoms	9	18
Without symptoms	10	20

Thus it can be seen that 80 per cent of 50 patients with hyperinsulinism had symptoms referable to the gastrointestinal system. Closer study of the symptoms of which the patients complained revealed that 33 or 66 per cent complained of epigastric burning, gnawing, fullness, flatulence, sourness, pain, or nausea. These symptoms occurring in the epigastrium are presumably of gastric origin. A more detailed account of the symptoms is summarized in table 2.

TABLE II

Gastrointestinal Symptoms Complained of by 50 Patients with Hyperinsulinism

	Number of Patients	Per Cent of Patients
Epigastric fullness, flatulence, burning, gnawing, sourness, nausea, pain	33	66
Vague "indigestion"	2	4
Abnormal hunger	1	2
Diarrhea	2	4
Constipation	1	2
Lower abdominal aching	1	2
Without gastrointestinal symptoms	10	20

Crenshaw [5] states: "The simultaneous occurrence of spontaneous hypoglycemia and peptic ulcer in the same patient is greater than expected on the basis of mere coincidence." From this study it seems that many of the symptoms are indistinguishable from those of peptic ulcer though ulcer was demonstrated in none of these cases, cases with peptic ulcer being purposely omitted.

Gastric Acidity: Levinson and MacFate [6] studied the free acid content in a large series of normal subjects and found the average to be 30 degrees on specimens obtained 15 minutes after alcohol stimulation, the method used with all patients in this series. It is believed that a greater number of patients would have shown excessive acid if determinations had been made at 30 and 60 minute intervals following stimulation.

It was found that 28 or 59.6 per cent of 47 patients who had gastric acid determinations made had acidities above the average normal of 30 degrees 15 minutes after stimulation. The average acidity of the 47 patients was 42 degrees.

A correlation between the degree of hypoglycemia and the increased acidity was attempted but the results were not striking. This is in keeping with the fact that different patients respond to a different degree to a diminished blood sugar level. This finding is summarized in tables 3 and 4.

TABLE III

Gastric Acidity Studies on 47 Patients with Hyperinsulinism

	Degrees Free HCl
Average of all patients studied	42
Average of 25 patients having blood sugar of 60 mg. per cent or lower during glucose tolerance test	45.8

Conversely, it can be shown that the patients with the highest acidities do not necessarily have the lowest blood sugars as shown in table 4.

TABLE IV

Blood Sugar Studies on Hyperinsulinism Patients with Normal and Excessive Gastric Acidities

	Milligrams Per Cent
Average lowest blood sugar of 10 patients with acidity of 60° or higher	58.5
Average lowest blood sugar of 17 patients with acidity of 30° or less	59.9

It would appear that the patient who presents himself for medical study, and who is found to have hyperinsulinism, is apt to have an increased gastric acidity which can not be closely correlated with the degree of hypoglycemia.

Roentgenologic Findings: It is believed that the fluoroscopic examination gives more reliable information concerning gastric motor function than any ordinary test. Although subject to error of interpretation, it is believed that on 50 examinations on patients with hyperinsulinism certain conclusions may be drawn. The findings are summarized in table 5.

TABLE V

Roentgenologic Findings in 50 Patients with Hyperinsulinism

	Number	Per Cent
Hypertonic stomachs	23	46
Hyperactive peristalsis	30	60
Spastic duodenal caps	16	32
Roentgenologically normal stomachs	9	18

It will be seen from the above figures that more than one abnormality occurred in the same stomach. It is believed that abnormalities are more numerous than would be found in the average run of the population.

DISCUSSION

Harris [7] first described spontaneous hypoglycemia and in an effort to give it a name having etiologic significance called it "hyperinsulinism." Later, he called attention to the digestive symptoms secondary to the disturbance in carbohydrate metabolism.[8]

Doubtless it is difficult to assess the extent of individual influences, such as physical constitution, living habits, nervous disposition, and carbohydrate metabolism, on abnormal gastric function. Deductive reasoning from the data presented above, however, leads one to believe that in a given instance the primary cause of abnormal gastric function is a derangement of carbohydrate metabolism.

One would wonder if the milk and cream feedings, most often used in the treatment of severe gastric symptoms, including those of peptic ulcer, did not have some effect on the production of hydrochloric acid in the stomach

as well as a local buffering action after the acid was already produced. Certainly a diet relatively high in fat and protein would tend to keep blood sugars from fluctuating so greatly as a carbohydrate diet. The resulting decrease in insulin production would cause less vagal stimulation and presumably less secretory and motor activity of the stomach.

If stimulation by insulin is a reliable test of vagal function, it seems logical to assume that vagal activity would be influenced markedly by endogenous insulin, particularly if insulin is produced in abnormally great amounts. It is believed the evidence presented would indicate that gastric function is largely dependent on carbohydrate metabolism with its influence on the vagal apparatus. This influence does not always manifest itself as markedly in one person as in another, but we believe that hyperinsulinism may be responsible for gastric dysfunction in a greater number of patients than is commonly realized.

Conclusion

Patients with hyperinsulinism are more apt than the normal person to have gastrointestinal symptoms. In a random collection of 50 patients with hyperinsulinism, 62 per cent had digestive symptoms which were responsible for their seeking medical care. An additional 18 per cent had symptoms which were elicited in the taking of the history.

Patients with abnormally low blood sugars during a six-hour glucose tolerance test tend to have increased gastric acidities which can not be correlated graphically with the degree of hypoglycemia.

Hypoglycemia is frequently associated with increased motor activity of the stomach.

Carbohydrate metabolism, through its effect on the vagal apparatus, plays a very important rôle in gastric function.

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A RECOVERY FROM ETHYLENE GLYCOL (ANTI-FREEZE) INTOXICATION; A CASE OF SURVIVAL AND TWO FATALITIES FROM ETHYLENE GLYCOL INCLUDING AUTOPSY FINDINGS *

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WE are reporting three cases of ethylene glycol (anti-freeze) poisoning, one of which survived. Very few, if any, reports of survivals have appeared in the literature, particularly with inclusion of studies of renal and hepatic functions. A recent article by Milles [1] may be referred to for an excellent survey of the literature.

The three patients, prisoners at a United States Army Disciplinary Barracks, consumed approximately 1200 c.c. of anti-freeze solution, the one who survived drinking 240 c.c., well over the minimal lethal dose of 100 c.c. as estimated by Hunt,[2] and the two who died consuming approximately equal portions of the remainder, about 480 c.c. each. Pons and Custer [3] describe a fatality following the ingestion of 200 c.c. of ethylene glycol.

CASE REPORTS

Case 1. On March 27, 1947, at about 1640 hours, a General Prisoner, 37 year old white male, was brought into the Dispensary with a history of having been drinking anti-freeze solution at intervals starting at about 1000 hours that day. He was very restless, irritable, talkative, speaking with a slurred speech, and was very ataxic. He presented the clinical picture of alcoholic intoxication but the odor of alcohol on his breath was absent. His pulse was rapid (100), respirations 28, pupils were of normal size and reacted to light, but there was slight injection of the conjunctivae.

His stomach was aspirated and material saved for toxicological examination. It was clear and did not have the odor of alcohol. His stomach was lavaged with a solution of 5 per cent glucose and 250 c.c. were left in. He was immediately put to bed but was still very restless and active, and had to be restrained to keep the intravenous needle in place. He was given 1000 c.c. of 10 per cent dextrose slowly, starting at about 2130 hours. At about the same time the patient became dyspneic and oxygen was administered via face mask. His blood pressure was 140 mm. Hg systolic and 100 mm. diastolic, pulse 120, respirations 32, at 2200 hours. At that time, he was unconscious. He was given caffeine-sodium benzoate (0.5 gm.) and coramine (2 c.c.) intravenously at 2230 hours. At 2300 hours, cogwheel respirations were noted and aminophyllin (0.25 gm.) was given intravenously. On March 28 at 0030 hours aminophyllin was repeated. At 0100 hours râles were heard in both lung bases. No jaundice or convulsions were noted at any time. At 0135 hours, patient was pronounced dead.

Pathology Report:

A. *Gross Findings:* Autopsy was performed 14 hours after death. The body was

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that of a well developed, well nourished, white male, whose body length was 72 inches and weight, 170 lbs. External examination was essentially normal.

Lungs: Pleural surfaces were smooth, glistening, and deeply congested. The lungs were extremely heavy. Section through the *right upper lobe* showed a prune colored moist parenchyma, in which the markings were almost completely obliterated. The *right middle lobe* was browner in color, but also moist and even emphysematous. The lung markings of the *right lower lobe* were completely masked by hemorrhagic edematous fluid. The *left upper lobe* on the upper aspect was similar to its fellow on the right. On the anterior aspect of the lower portion it was somewhat more air containing. The *left lower lobe* was wet, flabby and dripping with bloody fluid.

Heart: On the epicardial surface small pin point hemorrhages were seen particularly on the posterior aspect of the heart. The valve rings were of normal size. The aorta was normal. The myocardium was flabby, brownish red in color. The coronary arteries were normal. Heart weighed 350 gm.

Liver: Liver weighed 1800 gm. Capsule showed some small fibrous tags. On section the parenchyma was puffy and indistinct, yellow brown in color. Gall-bladder was normal.

Spleen: Spleen weighed 180 gm. It was flabby but essentially normal.

Adrenals: Normal.

Kidneys: Left kidney: Its capsule stripped with ease revealing a pale surface. It measured 11 cm. and weighed 150 gm. On section the parenchyma was deeply congested and averaged 22 mm., of which 7 to 8 mm. was cortical tissue. Pelvis was lined by a pale mucosa. *Right kidney:* Its capsule also stripped with ease, revealing a congested surface. It measured 11.5 cm. and weighed 150 grams.

Gastrointestinal Tract: Essentially normal. A few areas of congestion were seen in the stomach.

Head: The brain showed marked edema of the leptomeninges. The superficial vessels were congested. Sections through the brain revealed the moist structure noted on external examination. Cortex was moist, light tan brown in color. Examination of the basal ganglia, pons, cerebellum, floor of the fourth ventricle, and other portions of the base of the brain showed no unusual changes.

B. *Microscopic Findings:*

Leptomeninges and Brain: No evidence of hemorrhage or exudate was found in the subarachnoid spaces. Small and moderate-sized blood vessels in the brain substance were numerous, prominent, and congested in appearance.

Lungs: Dark granular pigment deposits were present in minimal quantities in the subpleural, peribronchial and perivascular spaces. The bronchi varied; some were empty, others contained erythrocytes. Many alveoli were filled with erythrocytes and edema fluid precipitate in variable proportions; and most alveolar wall capillaries were prominent and congested in appearance. A hilar node showed congestion of the vascular channels besides anthracotic pigmentation.

Heart: The subepicardial fat layer was relatively thick in one section and infiltrated between the superficial muscle bundles of the adjoining myocardium. The vascular channels were filled and prominent. The interstitial tissue was free of inflammatory infiltrate. The myocardial fibers appeared swollen, showing variable staining and fragmentation; with patchy areas lacking cross-striations. Bi-polar, brown, granular pigment was present in the vicinity of many muscle fiber nuclei. A moderate number of nuclei were relatively large and some were hyperchromatic.

Aorta: Not remarkable.

Liver: Triad areas were essentially negative, except for an occasional triad that contained a moderate lymphocytic infiltration. Liver cells showed degenerative changes, characterized by relatively swollen cells having coarsely granular cytoplasm, fatty vacuoles and in some instances absent nuclei. Sinusoids were blood filled and congested appearing.

Pancreas: There were scattered areas of degeneration, without signs of inflammation.

Spleen: There were several foci having the appearance of old fibrotic granulomata, with hyalinized vessels in their immediate vicinity.

Adrenal Gland: Pericapsular vessels were prominent and congested appearing. Cortical and medullary tissue was not noteworthy.

Kidneys: Capsule was not noteworthy. There was no increase in interstitial tissue, and no inflammatory infiltrate was present. All vascular channels were prominent, blood filled, and congested appearing. Glomerular capillaries were prominent and congested. Tubules showed cloudy swelling of the lining epithelium with granular cytoplasm and frequent absence of nuclei. Lumina contained minimal to moderate amounts of granular debris and many tubules contained *crystals* varying in shape from rectangular to polyhedral, to needlelike (figures 1, 1*a*, 1*b*, 1*c*).

Résumé: The gross findings included evidence of generalized congestion in the leptomeninges, brain, lungs, and abdominal viscera. Microscopically, the lungs and brain showed marked edema and congestion and generalized passive congestion was found in all viscera. The kidneys showed *crystalline deposits* in the tubular lumina, and degenerative changes in the tubular epithelium. The myocardium and liver showed cloudy swelling.

Toxicological Report: Toxicologic findings on the fluid suspected of having been ingested showed it to consist primarily of ethylene glycol (97.6 per cent), water (3 per cent), a trace of methyl alcohol (less than 50 mg./100 c.c.), coagulated organic matter and dye (0.4 per cent). This material was negative for ethyl alcohol and aldehydes. On fractional distillation the portions collected at 196 to 198° C. were found to have the chemical and physical properties of ethylene glycol. Chemical analysis of stomach washings showed a trace (less than 0.5 gm.) of ethylene glycol, and was negative for ethyl and methyl alcohol, aldehydes, and heavy metals.

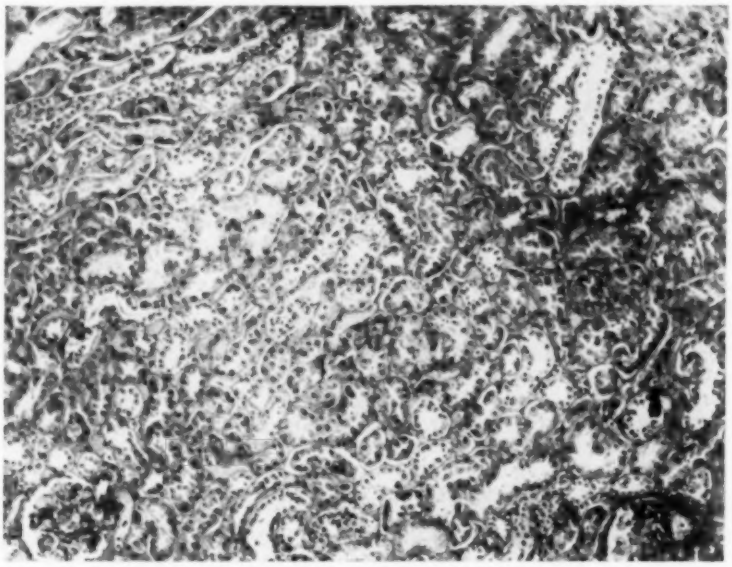

FIG. 1. Low power photomicrograph of kidney of case 1.

FIG. 1*a*. Low power photomicrograph of kidney under polarized light, showing doubly refractile calcium oxalate crystals of case 1.

FIG. 1*b*. High power photomicrograph of kidney of case 1.

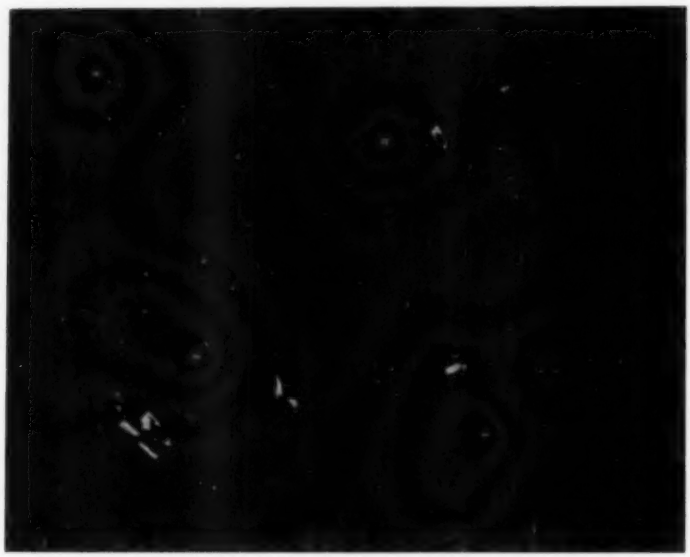

FIG. 1*c*. Same photomicrograph as figure 1*b* but under polarized light.

Analysis of samples of brain, liver, and kidney tissues showed ethylene glycol positive (slight trace); and was negative for barbiturates, non-volatile phenols, morphine and strychnine groups.

A quantitative analysis for oxalic acid showed 14.4 mg. oxalic acid per 90 gm. of mixed tissue.

With ethylene glycol found in the fluid suspected of being ingested, in the stomach washings and in the viscera, and with the gross and microscopical findings as listed above, the case is one of death due to ingestion of ethylene glycol.

Case 2. At the same time as case 1, another General Prisoner, a 24 year old Indian male, was brought in with the same history, having been drinking about the same length of time and the same amount. He appeared intoxicated, staggered, his motions were uncoördinated and his speech was slurred. He was very lethargic and appeared sluggish.

His stomach was lavaged with 5 per cent glucose and 250 c.c. were left in, after the stomach contents were aspirated. At 2030 hours he became dyspneic and oxygen was started via face mask. At 2100 hours, 1000 c.c. of 10 per cent dextrose were started intravenously. At this time patient lost consciousness. At 2200 hours, his blood pressure was 180/100, pulse 110, respirations 36. At 2230 hours caffeine-sodium benzoate (0.5 gm.) and coramine (2 c.c.) were given intravenously. They were repeated at 0120 hours on March 28. At 0320 hours his heart rate was rapid and irregular and râles were noted in both lung bases. Aminophylline (0.5 gm.) was given intravenously. No signs of jaundice or convulsions were noted. At 0328 hours, the patient died.

Pathology Report:

A. *Gross Findings:* Autopsy was performed within 13 hours after death. The body was 70 inches long and weighed 170 lbs. External examination was essentially normal.

Lungs: About 200 c.c. of clear serous fluid were present in the right pleural cavity and 500 c.c. on the left. The *right upper lobe* was soft and on cut section was reddish brown in color. The lobe was relatively air containing. A similar picture was present in the *right middle lobe.* The *right lower lobe* revealed areas of a deep bluish black color posteriorly. On cut section these areas were seen to extend within the parenchyma for some distance and a reddish brown fluid exuded from the surface. The rest of the lobe was light pink and air containing. The *left upper lobe* was soft and on the posterior aspect there were present, numerous large areas discolored a dark blue color. On cut section a reddish brown fluid exuded from the parenchyma. The *left lower lobe* was soft and also had numerous areas which were deep red brown in color and fluid exuded from the surface.

Heart: Over the pericardial surface were numerous pin point hemorrhagic areas. The valves were normal size. The aorta and coronaries were normal. The cardiac musculature was a deep red brown in color and was not enlarged.

Liver: The liver weighed 1750 gm. Parenchyma was a pale red brown color, but otherwise normal.

Spleen: The spleen was essentially normal except for slight congestion.

Adrenal Glands: Normal.

Kidneys: The *right* measured 10.0 by 5.0 by 3.0 cm. The capsule stripped without difficulty revealing a dark red parenchyma. On cut section the parenchyma measured 20.0 mm., of which 5.0 mm. was cortex. Cortical markings were well seen. The blood vessels appeared congested. The parenchyma was reddish brown in color. Calyces and pelvis of the kidney were not dilated. The *left kidney* measured 10.5 by 5.0 by 3.0 cm. The capsule stripped without difficulty, revealing a dark reddish brown parenchyma. On cut section the parenchyma measured 18.0 mm., of which 4.0 mm. was cortex. The parenchyma was reddish brown in color. Cortical markings were well seen. The calyces, pelvis and ureters of the kidney were without change.

Urinary Bladder: Urinary bladder contained about 1000 c.c. of clear yellow fluid (definitely not anuric).

Gastrointestinal Tract: Essentially normal.

Head: Brain was soft, edematous and congested. Circle of Willis was intact. On section of the brain the blood vessels were congested and the tissue was soft and edematous. The lateral ventricle, basal ganglia, cerebellum, medulla and pons were unchanged.

B. *Microscopic Findings:*

Leptomeninges and Brain: Subarachnoid spaces showed no evidence of hemorrhage; and a few scattered lymphocytes were present in the meninges. The subarachnoid vessels, as well as those lying within the brain substance, appeared prominent, blood filled, and congested. Sections of the cerebral cortex and cerebellar peduncle were otherwise not noteworthy.

Thymus: Normal.

Lungs: Lungs showed occasional areas of subpleural, peribronchial, and perivascular fibrosis. Minimal quantities of dark granular pigment were found in these areas. Intra-alveolar hemorrhage and accumulation of edema fluid precipitate were marked in some lung sections. This was associated with a minimal to moderate infiltration by polymorphonuclear leukocytes. Bronchi in these areas were partly filled with erythrocytes and edema fluid precipitate.

Heart: Venous channels in subepicardium, and the smaller vascular channels in myocardium were blood filled and congested appearing. The fat of the subepicardium extended into the adjoining myocardium and separated the muscle bundles. No increase in interstitial tissue or inflammatory infiltrate was present. Myocardial fibers showed some degenerative changes, characterized by swollen appearance of the

fibers, uneven staining, fragmentation, brown granular pigment deposits near the nuclei, and poorly defined cross-striations.

Liver: The capsule was intact. The usual lobular architecture was maintained. Triad areas were not remarkable. Sinusoids were packed with erythrocytes. Liver cells appeared swollen, having coarsely granular cytoplasm, with occasional vacuolization, and in some, the nuclei were not visible.

Spleen: Evidence of congestion.

Adrenals: Essentially normal.

Kidneys: Capsule was not noteworthy. Vascular channels were prominent, blood filled, and congested appearing. Interstitial tissue showed no increase in quantity, and no inflammatory infiltrate was present. Glomeruli showed congested capillary tufts. Tubules showed swelling of the lining cells, coarse granularity of cytoplasm, and absence of nuclei in some instances. Some of the tubular lumina were closed off; some contained amorphous eosin-staining debris; and many contained *crystals*, arranged in needle-like sheaves, in long slender parallelograms, and in irregular forms (figures 2 and 2*a*).

Prostate Gland: Normal.

Gastrointestinal Tract: Normal.

Résumé: The gross findings included cerebral and pulmonary edema, bilateral hydrothorax and generalized visceral congestion. Microscopically, marked edema and congestion of the lungs were found; a toxic nephrosis associated with crystal deposition in renal tubules and degenerative changes in tubule epithelium; cloudy swelling of myocardium and liver; and generalized visceral congestion.

Toxicological Report: Chemical analysis of the fluid suspected of being ingested showed it to consist primarily of ethylene glycol (97.8 per cent); water (3 per cent), coagulated organic material and dye (0.4 per cent), a trace of methyl alcohol (less than 50 mg./100 c.c.), and was negative for aldehydes and ethyl alcohol. Analysis of stomach washings was negative for ethylene glycol, ethyl and methyl alcohol, aldehydes and heavy metals. Analysis of brain, liver and kidney material yielded the following results: Ethylene glycol positive (slight trace), but negative for barbiturates, non-volatile phenols, morphine and strychnine groups. Quantitative analysis of tissues showed 23.5 mg. oxalic acid per 90 gm. mixed tissues.

Case 3. At 1645 hours on March 27, 1947, a 19 year old white male, General Prisoner, was brought into the Dispensary with a history of having ingested antifreeze solution about 1400 hours that afternoon. He appeared acutely intoxicated, acted and spoke euphorically, was aggressive, very talkative and active. He was also very ataxic. The stomach was aspirated and lavaged with 5 per cent glucose and saline about 1715 hours. He remained ambulatory, was talkative and restless until about 2100 hours when he quieted down and was put to bed. At that time 1000 c.c. of 10 per cent glucose and saline were started intravenously. At 0100 hours on March 28, although patient was only slightly dyspneic (respirations 28), prophylactic administration of oxygen was instituted and maintained throughout the morning and the next day. Caffeine-sodium benzoate (0.5 gm.) and coramine (2 c.c.) were given at about 0200 hours. At this time he was stuporous, and moved only on painful stimulation.

At 0530 hours, pulse was 100, respirations 28, blood pressure 120/90. He appeared somewhat more comfortable and responsive. About 0600 hours 1000 c.c. of 5 per cent dextrose and saline were started slowly. At 0800 hours he appeared somewhat more dyspneic, rectal temperature was 100.4° and pulse 120. His bladder was palpable, but he urinated in bed before catheterization could be attempted. Penicillin 80,000 units intramuscularly was given prophylactically at 0900 hours. At 1000 hours an enema was given with good results. He appeared much more alert and responsive after this. At 1100 hours urine specimen showed two plus albumin, spe-

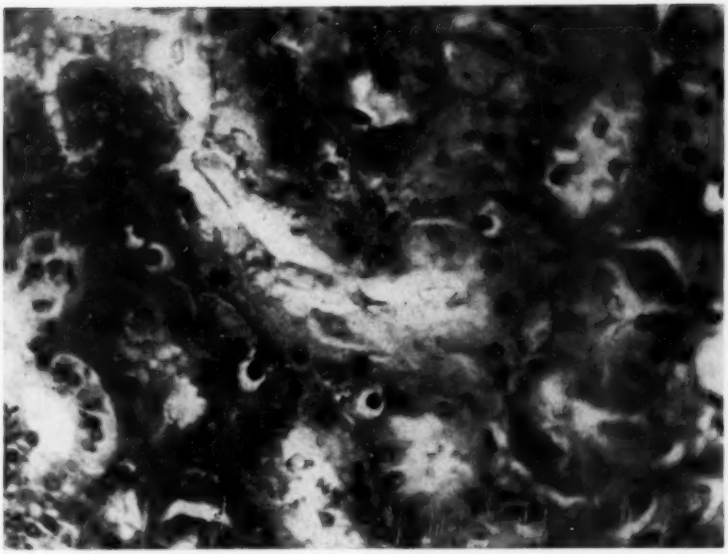

FIG. 2. Photomicrograph (high power) of section of kidney of case 2.

FIG. 2a. Same photomicrograph as figure 2 but under polarized light.

cific gravity of 1.008, with an occasional granular cast but was negative otherwise. Beginning at 1200 hours, 30,000 units of penicillin were given intramuscularly every three hours. At 1300 hours, his pulse was 108, respirations were 28, blood pressure was 142/104. At this time a few râles were heard in the left lung base. He was propped up in the bed with a back rest. At 2000 hours 500 c.c. of plasma were given slowly.

On March 29 at 0800 hours, pulse was 84, respirations 22, oral temperature 98.6°, blood pressure 148/80. He was comfortable in bed, talkative, asymptomatic, except that he could tolerate only small sips of water or ice chips without vomiting. The oxygen and parenteral fluids had been discontinued that morning. The penicillin was discontinued at 1200 hours March 30 (a total of 560,000 units). On March 31, his urine showed two plus albumin and a few coarsely granular casts. His blood pressure was 148/88. Temperature, pulse and respirations were normal. He was maintained on small, frequently administered liquid feedings. On April 1 the urine showed three plus albumin, many granular casts, specific gravity of 1.011, and was negative for sugar and acetone. On April 2 urinalysis revealed three plus albumin, many granular casts, was negative for hemoglobin, red cells or sugar. His blood pressure was 170/100 and his fundi showed constriction of the arterioles. At this time, although the patient was asymptomatic he was transferred to a Station Hospital for further and more detailed investigation of the abnormal urinary findings and the elevated blood pressure and such further therapy as might be deemed necessary.

On admission to the Station Hospital, he complained of anorexia, weakness, and a frontal headache relieved by aspirin. He stated he had vomited that morning and had had a bloody nose shortly thereafter. The physical examination was negative except for tenderness on palpation over the renal areas, blood pressure 176/118, and slight constriction of the arterioles of the fundi. The patient was voiding freely and the urine showed a pH 5.0, specific gravity 1.004, albumin one plus; sugar and microscopic were negative. In the following 24 hours, the urinary output was 2500 c.c. with a fluid intake of 3080 c.c. Blood chemistry values are shown in the table, and it will be noted that on April 3, blood phosphorus was 7.4 mg. per cent, non-protein nitrogen 158 mg., urea nitrogen 42 mg., and creatinine 3.8 mg. per cent, comprising

Table I

Studies of Renal and Hepatic Function (Case 3)

Date	April 3	4	7	10	14	May 1
Blood						
NPN	158	182	111	75	41.6	43.5
Urea N	42	73	53	36	18.3	16.1
Creatinine	3.8		3.3	1.76	1.6	1.5
Sugar	125					109.9
Chloride	439				470	478
Cholesterol	167				151	150
Phosphorus	7.4		7.96	3.7	3.57	3.18
Calcium	9.1		9.4		10.8	
CO_2	50.4				54	
Van den B (Direct)	Neg.				Neg.	Neg.
Van den B (Indirect)	0.2				0.2	0.2
Bromsulfalein	3%—45 min. 0—60 min.				2½%—45 min. 0%—60 min.	No dye—45 min.
Total protein	8.55				6.71	
Albumin	5.28				3.95	
Globulin	3.27				2.76	
A/G	1.63/1				1.64/1	
Ceph. flocculation	Neg.—24 hrs.				Neg.—24 hrs.	
Alkaline phosphatase			2.5 BU		2.85 BU	

a uremic state. Liver function tests were all normal including a urine Sparkman urobilinogen of 6.97 mg. per cent (normal is less than 8.0 mg.). Patient was placed on a low protein diet which he retained without difficulty. Amphojel and calcium carbonate were given orally, and fluid intake by mouth was adequate to provide a good urinary output.

It will be noted from the table that over the next few weeks the elevated blood chemistry values reverted to normal and all tests indicated not only the return of kidney function but continued normal liver function. On April 12 the blood pressure was 135/85, his eye grounds were normal, visual fields were normal, as was the electrocardiogram. The red cell count was 4.57; hemoglobin, 15 gm.; and white blood cells, 7500. Kahn and Wassermann tests were negative. X-ray of the heart and lungs showed slight enlargement of the heart according to Ungerleider's table but it was felt that it was within the upper limits of normal.

On May 2 he was transferred back to the Disciplinary Barracks. At that time his blood pressure was 125/75, his urine was completely negative, and he was able to concentrate up to 1.025 and dilute to 1.004. His fundi were normal as was his complete physical examination. He was asymptomatic and went back to duty. It is our opinion that he has completely recovered.

Comment

It is believed that the early administration of oxygen, supportive therapy, his age, and physical stamina were contributing factors in the survival of this patient. However, the quantity of ethylene glycol ingested and the short period of time that elapsed between the ingestion of the solution and the institution of therapy were probably the most significant factors. Treatment was begun in three hours in the case of the survivor as contrasted with six to seven hours in the fatal cases. Each of the fatal cases consumed nearly twice as much ethylene glycol as the patient who recovered. The return of his renal function to normal indicates that the kidney damage was not irreversible.

Discussion

Apparently three stages occur in ethylene glycol intoxication, namely: (1) cerebral, (2) pulmonary, and (3) renal. Death may occur in any of the three stages depending on the severity and reversibility of the tissue damage. These stages should be watched for and expectant and prophylactic treatment instituted as soon as possible.

(1) The first stage is manifested (clinically) by a period of stimulation simulating acute alcoholic intoxication, followed by coma; (pathologically) by cerebral edema.

(2) The second stage is usually the final cause of death and is manifested (clinically and pathologically) by pulmonary edema.

(3) If the patient survives these two periods, the third stage becomes prominent and is manifested clinically by an acute nephritis-like state with hypertension and signs of renal insufficiency and uremia which may or may not (as evidenced in this case), but usually does, terminate in death. However, it is difficult to correlate the calcium oxalate crystal *nephrosis* seen

pathologically with the *nephritis*-like clinical state (except for the absence of red blood cells in the urine). No satisfactory explanation can be presented at this time.

Due to the extreme toxicity of ethylene glycol, we agree with preceding authors, that anti-freeze solutions containing this chemical should be plainly marked as poisonous.

Summary

1. We have presented two fatalities and one case of survival from ethylene glycol intoxication.

2. Apparently there are three stages in its course: cerebral, pulmonary and renal. Death may occur in any of these stages.

3. Early therapy is necessary for survival.

4. Solutions containing ethylene glycol should be labeled as poisons.

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CALCIFIED CARDIAC ANEURYSMS *

By A. Bogoch, M.D., and E. F. Christopherson, B.Sc., M.D., F.R.C.P.(C), *Vancouver, B.C., Canada*

The term cardiac aneurysm was first used to signify general enlargement of the heart cavities, but in recent years it has been reserved for local pouches or sacs in the heart wall.[1] Combining reported data, Parkinson, Bedford and Thomson [2] state that cardiac aneurysm occurs in 9 per cent of cases of cardiac infarction examined at necropsy. Other observers [3] report an incidence of 37 per cent, but they must include, as Crawford [4] points out, even small indentations of the endocardial wall at the site of an old infarct. He feels that the term cardiac aneurysm "should be confined to a permanent localized bulging, or during systole, a well marked localized expansion beyond the contour of the rest of the heart."

In the majority of cases, cardiac aneurysms follow myocardial infarction. The remaining few are due to syphilis (gumma), bacterial infection (abscess or embolus), rheumatic myocarditis; or are of congenital or traumatic origin. In 1939, Gubner and Crawford [5] demonstrated, by roentgenkymographic studies, that bulging takes place during systole in a large number of cases of coronary occlusion with infarction. As healing with fibrosis progresses, the intraventricular pressure may cause the formation of a cardiac aneurysm unless the scar becomes strong enough or is reinforced by mural thrombi and adherent pericardium. The left ventricle is almost exclusively affected and the anterior and left wall of the ventricle near the apex is more than twice as commonly involved as the posterior wall. Rarely is the upper part of the intraventricular septum the site.[1] The aneurysm is usually not sharply demarcated from the main ventricular cavity, but it may be saccular and communicate with the cavity by a definite neck or orifice. It varies from a few cm. up to a dilatation equal in size to the remainder of the ventricle. The pericardium over the bulge is often adherent and the interior of the sac usually contains thrombus which may be laminated and organized. As a rule, the remainder of the heart is enlarged, and study of the coronary arteries reveals occlusion of the branch supplying the involved area, and varying degrees of sclerosis in the other branches.[6]

Calcification in the wall of such aneurysms is a relatively uncommon occurrence. Jaksch-Wartenhorst [7] in 1928, described a case in which an intracardiac shadow near the apex, seen radiographically, proved to be a calcified clot within an aneurysm. In 1932, Determann [8] was the first to recognize calcification in the wall of the sac by roentgen-rays during life. Hochrein [9] described a case in 1937, and Parkinson, Bedford and Thomson [2] added three more a year later. Since then, very few cases of calcified

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cardiac aneurysm have been recorded.[10, 11, 12, 13, 14] Recently we have had the opportunity of studying the development of calcification in two cases, the histories and findings of which follow:

Case 1. A 65 year old white male suffered a cerebrovascular accident in July, 1945, resulting in a left hemiplegia which confined him to bed until he died of a sub-

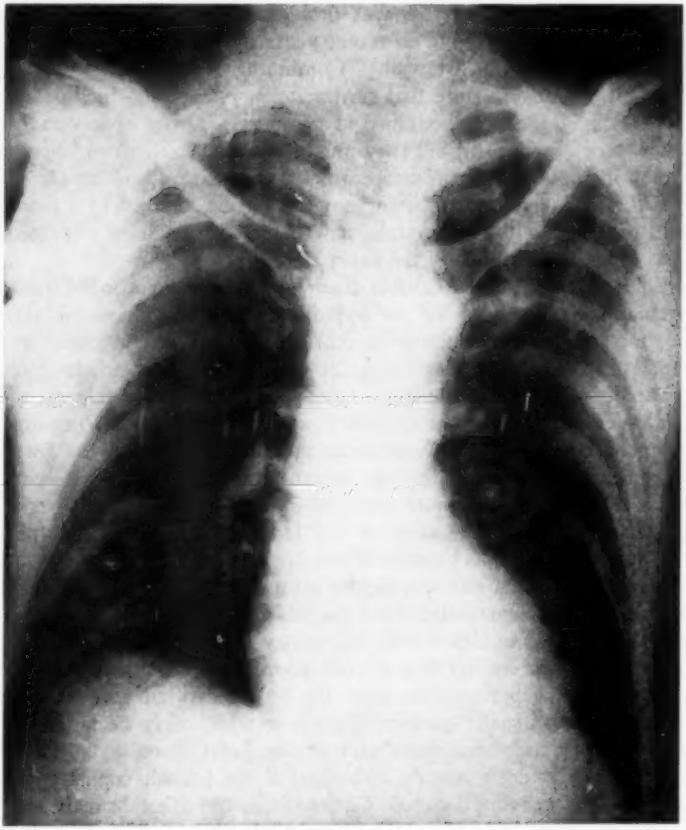

FIG. 1.

sequent right hemiplegia in March, 1948. There were no cardiac symptoms, nor was objective evidence of heart disease developed clinically. Pulse, 80 per minute and regular, blood pressure 150 mm. Hg systolic and 90 mm. diastolic. No electrocardiographic studies were made. Except for several febrile episodes which were diagnosed as recurrent bronchitis, his course in hospital was unremarkable. On August 15, 1946, during one of these illnesses, portable roentgenograms of the chest were taken, and revealed only scattered fibrosis and calcification of both lung apices

(figure 1). Stereoscopic postero-anterior chest films on February 20, 1947, revealed a semi-lunar shadow outlined by a thin eggshell margin of calcification which lay over the apical region of the heart above the dome of the diaphragm (figure 2). Physical examination of the chest on April 22, 1947, was reported as negative, and two days later, roentgen-rays (figure 3) showed the calcified area to be slightly more prominent than previously. In the left lateral view on April 29, 1947, it was seen

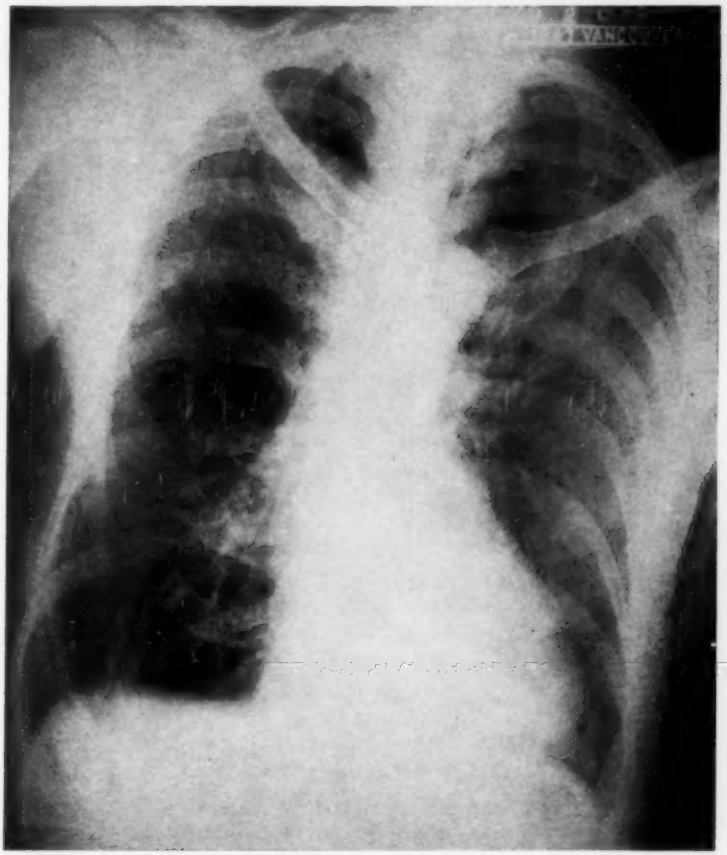

FIG. 2.

to lie well anteriorly, almost at the anterior limit of the cardiac shadow, but within the confines of the heart (figure 4). By September 30, 1947, the shadow was circular, well outlined by calcification, and about 4 cm. in diameter (figure 5). Thus, it would appear that roentgen-ray examination of the heart, negative on August 15, 1946, revealed a semi-lunar area of calcification on February 20, 1947, which became

more sharply delineated to form a circular shadow about 4 cm. in diameter and which appeared to be associated with the right ventricle.

Necropsy revealed the immediate cause of death to be acute bronchopneumonia and cerebral softening. There was generalized arteriosclerosis.

Heart (450 gm.). The anterior wall of the left ventricle near the apex was expanded by a stony hard globular mass with a smooth contour covered with thickened

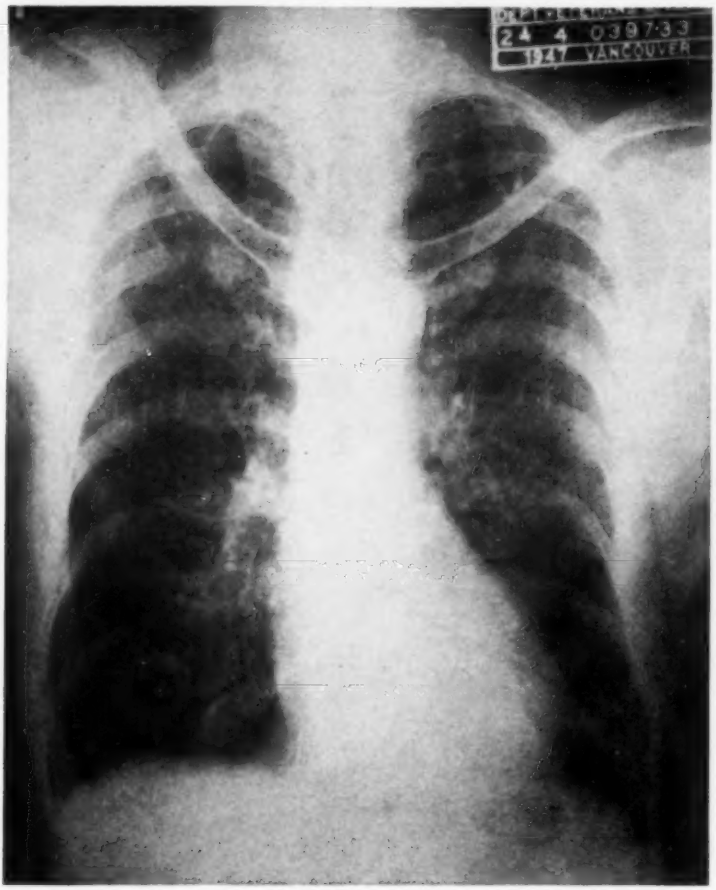

FIG. 3.

visceral pericardium. On section, it resembled a tuberculoma, being circular in outline and having a yellow color. Its central portion appeared pultaceous while its wall was densely calcified having the consistency of bone. It measured 3 cm. in diameter and occupied the distal third of the anterior wall of the left ventricle and

the adjacent septum. The wall of the mass appeared to be fibrosed myocardium measuring 2 to 5 mm. On the endocardial surface overlying the mass was an organized thrombus, while the septum above it was thinned and fibrotic. The mass was interpreted as being an old infarct with aneurysm formation, thrombosis and calcification. Although the coronary arteries were carefully searched, the site of occlusion was not found. Histologic examination confirmed the above interpretation and

FIG. 4.

showed the central necrotic material to be amorphous debris containing cholesterol clefts. The wall consisted of dense fibrous tissue showing calcification and encompassing small bundles of myocardial fibers.

The *brain* weighed 1150 gm. and the vessels at the base showed advanced atherosclerosis. The frontal lobe of the right hemisphere and the anterior portions of the basal ganglia were occupied by multiple small cyst-like spaces, the result of old softenings. These measured from 0.5 to 1 cm. in diameter and some communicated

with the anterior horn of the right lateral ventricle. The remainder of the internal capsule and portions of the parietal and occipital lobes showed irregular patches of recent softening. In the left hemisphere, an area of recent softening measuring 3 cm. in diameter involved the anterior limb and genu of the internal capsule.

Case 2. An 80 year old senile male was active as a warehouseman until the spring of 1938, at which time he experienced an attack of coronary thrombosis. Ac-

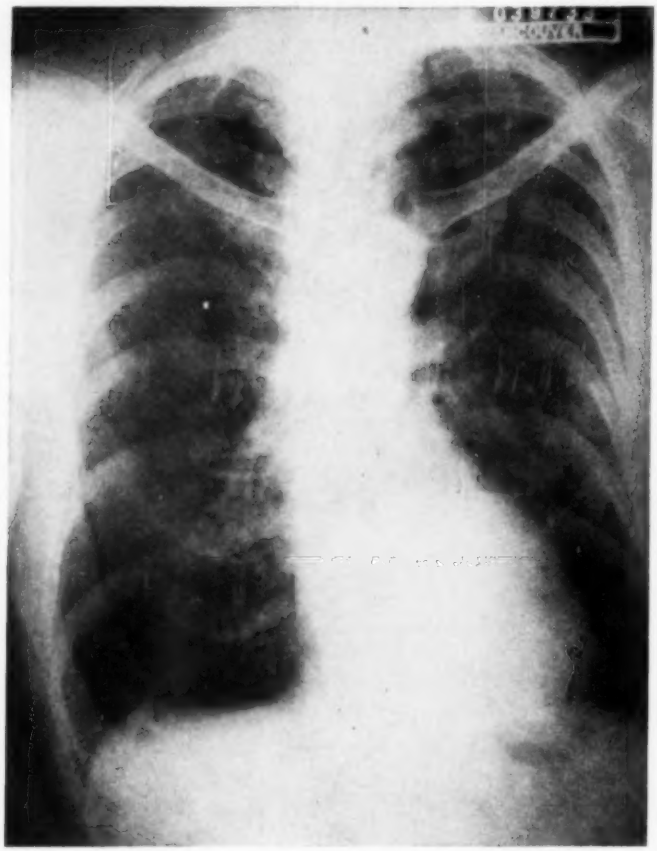

FIG. 5.

cording to accurate reports, he remained at complete bed rest for six weeks. In spite of the diminished exercise tolerance that followed this illness, he was able to climb scaffolding while supervising painting in a shipyard during part of the World War II. On January 4, 1944, he was admitted to hospital with moderately severe congestive heart failure, from which he soon made a good recovery. When seen last, on November 17, 1948, he felt well and was able to walk for long distances on level ground, but

became dyspneic on climbing stairs. His peripheral vessels were somewhat tortuous and sclerotic. Marked varicosities of both thighs and legs, and moderate pitting edema to the level of the upper third of each leg, were noted. The apical impulse was just outside the midclavicular line in the fifth left interspace, heaving and moderately diffuse. The rhythm was regular except for occasional extrasystoles, and the heart sounds were of normal intensity. A grade one late mitral systolic murmur propagated to the axilla was present. The blood pressure was 120/60 in the right arm, and 110/60 in the left. With the exception of mild bilateral conduction deafness and moderate senile pulmonary emphysema, the remainder of the physical examination was negative. Routine blood work and urinalysis revealed no abnormalities, and the total serum cholesterol was 235 mg. per cent.

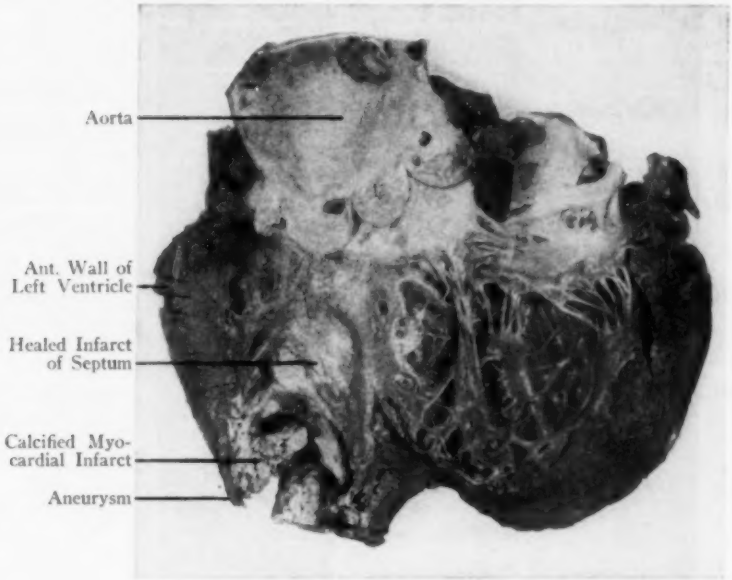

FIG. 6.

Recent electrocardiograms revealed findings similar to those noted in the earliest available tracing of February 27, 1939 (figure 7). Portable chest roentgenograms taken when he was admitted in congestive failure (1944) revealed thickened pleura, fibrosis and calcification of the right upper lung, probably from old tuberculosis, with deviation of the trachea to the right. Increased markings extended from both hila, and the heart was slightly enlarged (figure 8). On February 2, 1945 (figure 9) a bulge in the contour of the left ventricle was noted, and linear calcification just inside the lower left border of the heart shadow associated with bulging in this region was visible on March 3, 1947 (figure 10). Ledging of the upper margin of the aneurysm on the anterior contour of the heart was demonstrated in a right anterior oblique film taken September 21, 1948 (figure 11). On fluoroscopic examination, the aneurysm moved very little, but did so synchronously with the rest of the ventricle.

Discussion

According to Diamond [15] calcification of the myocardium is always secondary to necrosis or degeneration of toxic, inflammatory or vascular origin, the latter being commonest, as in the two cases described. Such calcifica-

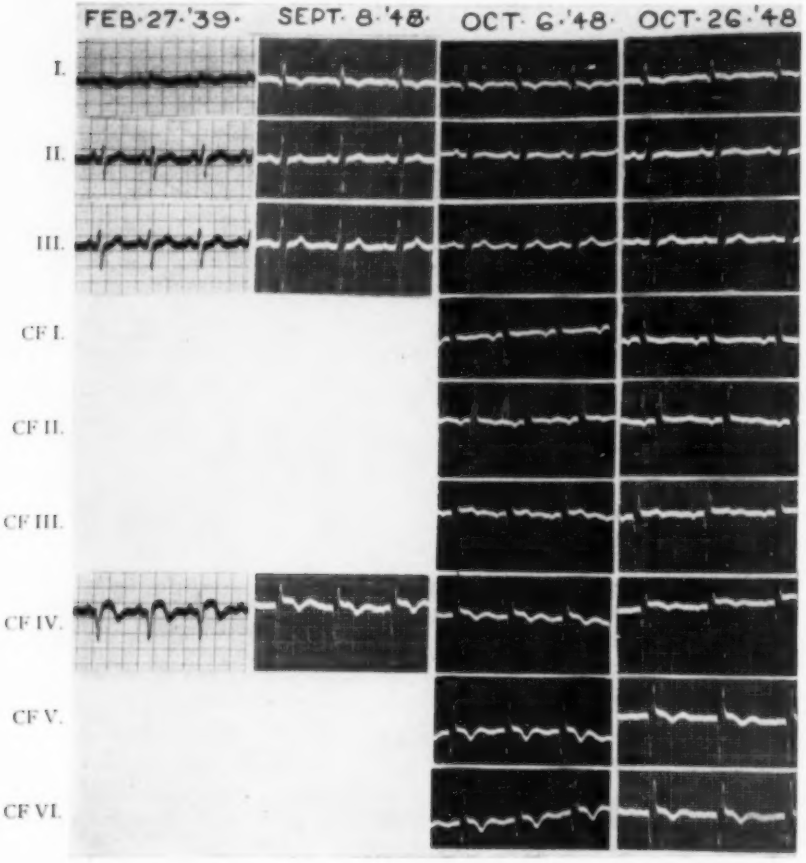

Fig. 7.

tion involving the laminated clot or the wall of the sac is an invaluable radiologic aid in the diagnosis of cardiac aneurysm. Calcification of a cardiac aneurysm has to be differentiated from calcified pericardium such as may occur in constrictive pericarditis. In aneurysm, the calcified shadow is usually linear, limited to the left ventricle, and situated within the heart

contour. Pericardial calcification produces a thicker and more irregular shadow not restricted to the left ventricle and situated outside the heart contour. Calcification may become evident radiologically within a short period of time as demonstrated in the first case. This is in contradistinction to a recent report by Penner and Peters [18] of a patient who experienced a myocardial infarction 15 years previous to the diagnosis of a calcified cardiac

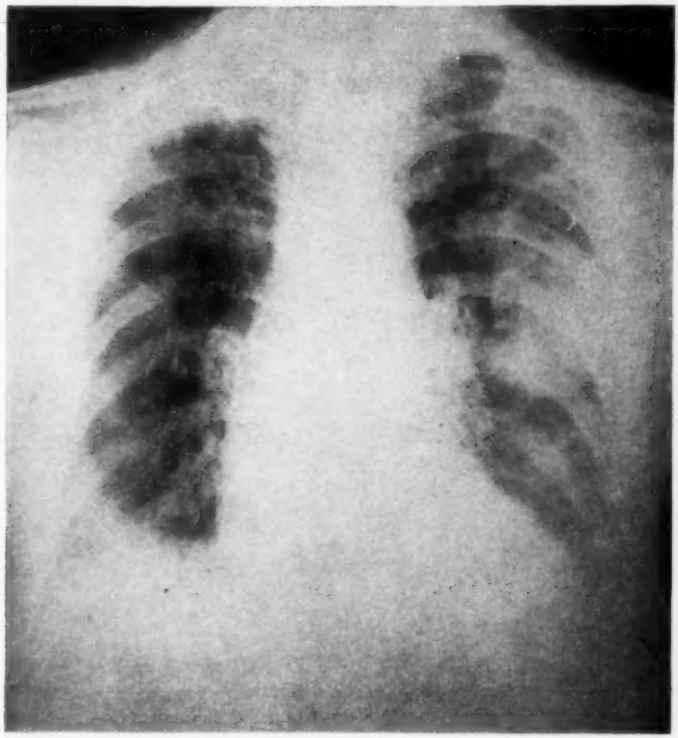

FIG. 8.

aneurysm, and in which they state that "the calcification must have been many years in development."

The diagnosis of cardiac aneurysm is difficult, inasmuch as the symptoms and clinical findings are so indefinite. In the majority of cases, there is a history pointing to a previous attack of coronary occlusion, and often of an inadequate period of bed rest.[16, 17, 18] When symptoms are present, they are those of heart failure. According to Berk [10] these patients frequently have repeated attacks of congestive failure and compensation is difficult to re-

establish. Crawford [4] feels that the aneurysm itself does not appear to alter the clinical course, in most instances the deciding factor appearing to be the functional capacity of the rest of the ventricle. Some are surprisingly well and are able to carry on a comparatively active life.

A valuable physical sign described by Libman and Sacks [19] is the presence of an abnormal palpable pulsation separate and distinct from the apical

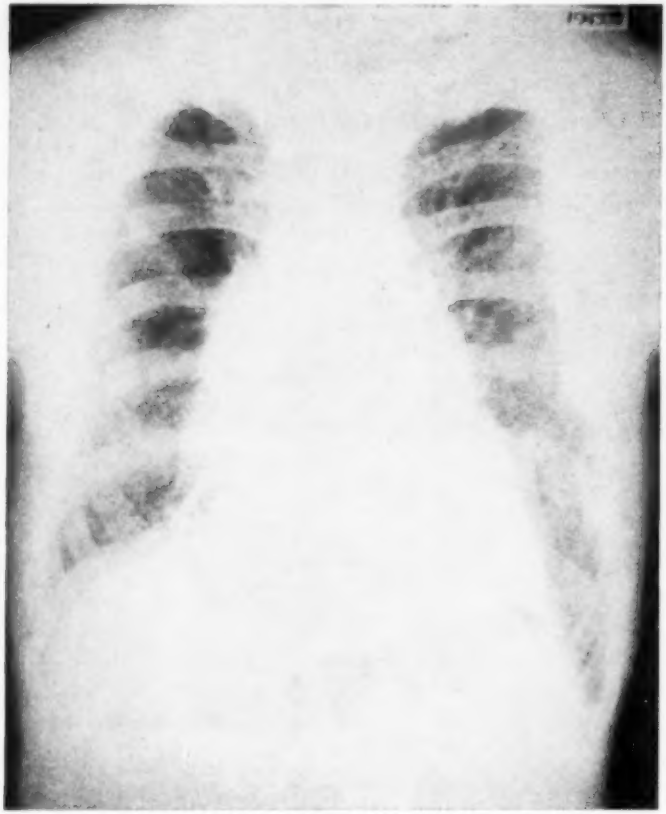

FIG. 9.

pulsation, and situated between the apex and the sternum. It was present in five out of 13 cases described by Crawford,[4] but is a less common finding according to other authors.[2] Libman [20] also emphasized the importance of a weakly palpable or impalpable apical impulse and a poor first apical heart sound, found associated with the abnormal pulsation. In the majority of

cases described by Parkinson, Bedford and Thomson,[2] the apical impulse was displaced outwards, was more diffuse than normal, and often unduly forcible or heaving. However, this is a common finding unassociated with cardiac aneurysm. According to Gross and Schwedel,[6] the presence of a large apical impulse and disproportionately poor heart sounds, is a sign of limited value, since on a number of occasions when they suspected the diag-

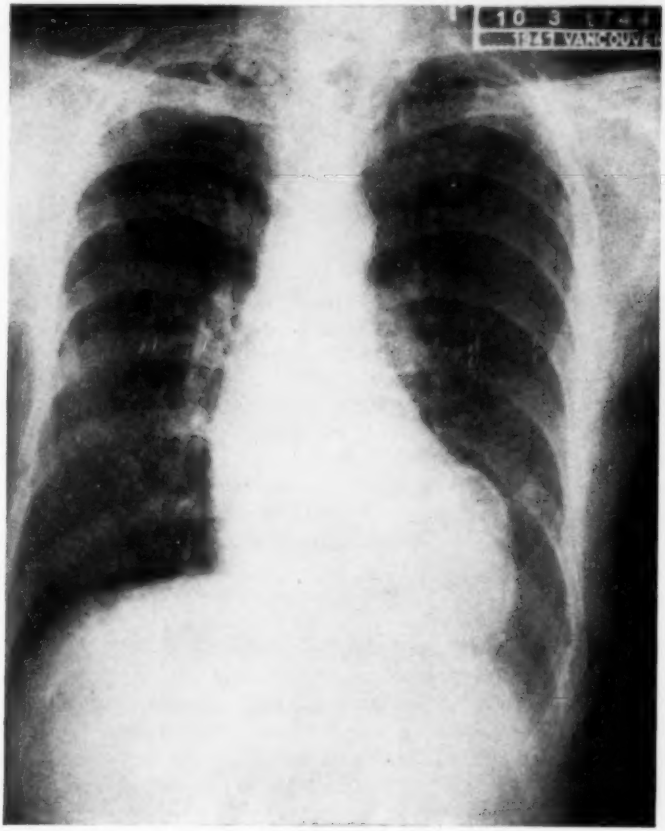

FIG. 10.

nosis on the basis of this disparity, no aneurysm was found. Many different physical signs have been described, including various murmurs and arrhythmias, but a careful review of many of the cases reported reveals that these are of little or no aid in the diagnosis. The blood pressure is variable,

and Parkinson, Bedford and Thomson [2] found the average to be 130/70 in 45 cases collected from the literature.

Electrocardiographic tracings usually reveal evidence of a preceding myocardial infarction, and may assist in localizing the lesion in the anterior or posterior part of the ventricle. These alterations may [18] or may not [6] be

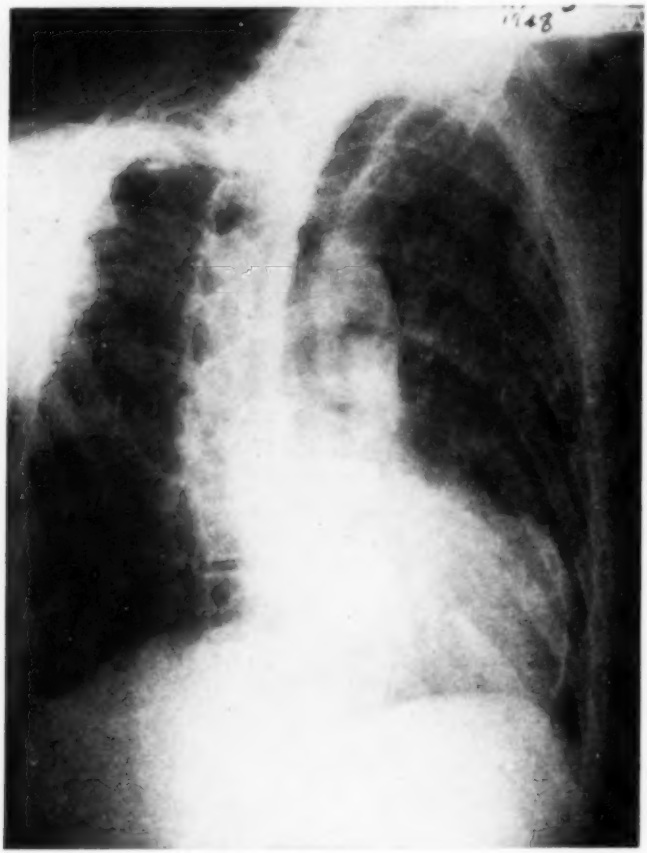

FIG. 11.

constant over months or years. Several patterns have been described but none is characteristic of an aneurysm of the heart. However, the presence of right axis deviation has been reported in six out of 22 cases discussed by Eliaser and Konigsberg,[21] and of 29 cases described by Gross and Schwedel,[6] in addition to three who showed this feature, another three later developed a

shift from left to right axis deviation. In view of the rarity of occurrence of right axis deviation in patients with hypertensive or arteriosclerotic heart disease,[22] in the absence of other known causes, this pattern may be considered a presumptive sign of cardiac aneurysm. Right axis deviation in the presence of left ventricular enlargement is unexplained, but may be due to enlargement of the right ventricle as a result of congestive heart failure [6] or to displacement of the anterior longitudinal sulcus and right ventricle to the right by the distended anterior wall of the left ventricle. The presence of the above noted displacement in some cases of cardiac aneurysm has been stressed by Dressler and Pfeiffer.[18]

The diagnosis of cardiac aneurysm depends largely on radiologic examination. The heart is usually, though not always, enlarged to the left, and because the aneurysm often involves the lower half of the left ventricular contour, the apex appears broadened or blunted, giving the heart a square or rectangular appearance.[2] It is often difficult, however, to differentiate this from the heart seen in hypertension or aortic insufficiency. The most characteristic finding is a localized bulge occurring anywhere in the contour of the left ventricle. An aneurysm of the anterior wall is clearly seen in the right anterior oblique position, in which case the upper margin forms an abrupt ledge or shelf on the anterior contour of the heart,[2] and this feature is well demonstrated in case 2. An aneurysm of the posterior wall is best visualized in the left anterior oblique position. Posterior wall aneurysms may displace the esophagus. Apical aneurysms may be difficult to visualize because the bulge may lie against the diaphragm and be obscured by its shadow, but fluoroscopic examination with the diaphragm fully depressed in full inspiration will aid visualization. The pulsations of the aneurysm may be noted on fluoroscopy and recorded by kymography. They may be strong or weak, synchronous or asynchronous, systolic or contrapulsile, but in the majority of cases asynchronicity with contrapulsile pulsation is present.[6] The presence of calcification as an invaluable aid in diagnosis has been noted above.

The average period elapsing between the initial attack of coronary thrombosis and death in seven patients with cardiac aneurysm reported in one series [2] was 23 months. Death is usually due to congestive heart failure or to further coronary artery occlusions. Rupture of a cardiac aneurysm is a very rare occurrence.[23] Some succumb to cerebral embolism from a dislodged fragment of clot, as apparently occurred in the first patient discussed above.

Summary

Two cases of calcified cardiac aneurysms are reported, and the clinical aspects of cardiac aneurysm are briefly reviewed.

We wish to express our thanks to Dr. H. E. Taylor, Director of Pathology, Shaughnessy Hospital, for his help in the preparation of this paper.

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THE DOCTOR AS CITIZEN *

By Henry Allen Moe, *New York, N. Y.*

When, to fulfill the promise made in response to your president's persuasive and friendly charm, a man like me sits down at his table to consider what he may say that will be worth a half-hour of your time at the end of several busy and intellectually full days, he really has a question to answer. What can a man possibly say that many, perhaps most, among you could not say better, have not thought about more cogently? What is there of thought about "The Doctor as Citizen" that a lawyer, as I am, and an executive officer of a foundation may express with any validity that this distinguished audience would recognize as valuable?

In your science, in your practice of the healing arts, in your search for new truth, doubtless things go well, and though doubtless not as well as you would hope, still you move forward. Science has its method for going forward; and you know the method: you do not know all the methods but the larger aspects of the method of science you do know.

Once outside your science, however, outside in the world of value where you live most of your lives, you are like the rest of us. All of us are asking ourselves all sorts of questions that we cannot answer, yet which we feel we ought to be able to answer and which we know we must answer, else our professional attainments will hardly count in the future and certainly give us no satisfactions.

Perhaps, I said to myself, I might, with profit, discuss some of these matters with you: perhaps my experience, a distillation of my experience, so different, I should suppose, from yours may have validity enough to go into your thinking. I ask you to believe that this is said very modestly: it may or may not be so. Of that you may judge when I have done.

I started from the premise that what distinguishes the professional man is that he has a history, a history in his profession, and a concern, as the Quakers say, for the future. For you, some of that history and some of that hope is embodied in the pledge you all have made upon being admitted to the Fellowship of this College. But this is a very small part indeed of the history and the hope which the medical profession has long maintained. As citizens we are all laymen; as professionals we are all citizens; and only as citizens, of whatever form of government, do we, as professionals, fulfill our deeper hopes, have our chance of success, exercise our motives, and live our lives. This is my theme: The Doctor as Citizen is conscious of history and he has a concern for the future.

The thought of the citizen in these days is dominated by the cliché that there is "so little time," or expressed in another way, "it is later than

* Convocation address, Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

you think": we are going to Hell fast, the clichés all affirm, and we have got to do something about it *fast*. Perhaps so; but we, as professionals, cannot do anything about it fast—not a thing. Perhaps government can; but we cannot. Perhaps any government, in any present, can only skirmish on the battle lines of civilization, perhaps only fight holding actions—important holding actions to be sure, but none-the-less only holding actions. Perhaps the real battle is ours to fight; perhaps the slow gain called progress is ours to make. It is, I think.

A few examples from our long history that, in the relationship of man to man, things do not happen fast, seem worth mentioning:

When Julius Caesar parleyed with the German King Ariovistus on the Rhine in 58 B.C., Ariovistus told Caesar that he had not made war on the Gauls but they upon him and, as for the host of Germans he was bringing over into Gaul, his object was to protect himself, not to attack Gaul; that his warfare had been defensive not offensive. He had crossed the Rhine, he said, not of his own desire but upon the request and summons of the Gauls.

The colloquy, you see, might well have been between Hitler and Petain seven years ago.

When John Lloyd Stephens, New York lawyer and engineer, travelled from Odessa to Moscow in 1835—the first American to do so, I believe—he observed, "It is almost impossible for an American to believe that even in Russia he incurs any risk in speaking what he thinks; he is apt to regard the stories of summary punishment for freedom of speech as bugbears or bygone things. In my own case, even when men looked cautiously around the room and then spoke in whispers I could not believe that there was any danger. Still, I had become prudent enough not to talk with any unnecessary indiscretion of the constituted authorities. . . ."

What Stephens wrote more than a century ago might, as you see, have been written by any American traveller yesterday; and indeed is being written now by Anna Louise Strong in her series of articles, "Jailed in Moscow" appearing daily in *The New York Herald Tribune*.

Things change slowly in the hearts and minds of men and we should not expect anything in the relationship of man to man to happen fast: if we do, we miscalculate. For, assuredly, they will not happen fast.

Still, things do happen. There was spoken the Sermon on the Mount, and thereafter there was some mitigation of man's inhumanity to man. Not so much as Christ hoped, but some; and even at Buchenwald they knew their inhumanity was wrong. To have made all men aware of that is no small thing.

For example of how things happen in the relationship of man to man, I turn naturally to an example from the history of the law. The scene is France in the 10th century A.D. Men were aware of the Sermon on the Mount; the brotherhood of man, then as now, shone as an ideal before good and thinking men. Yet rapine and loot and robbery were not, could not be,

quelled. There was no law powerful enough to restrain; for the right of such warfare had become the distinctive, recognized privilege of those with power enough to exercise it. But scholars, as we should call them now, with the ideal of the Sermon on the Mount before them, could not be content with things as they were. Legislative attempts to limit the range of the blood feud had been tried; ex-communication as a punishment for sacrilege was not new; nor was the privilege of sanctuary an innovation. Even a special care for the defenseless was not new. But none of these concepts and measures brought peace to the highways. What the scholars did, in their efforts for peace, was to make a fusion of old elements in a conscious endeavor to mark off by general definitions a sphere of peace from the surrounding sphere of feud, so that peace itself, and for its own sake, became the object to be aimed at. Thus, from the Sermon on the Mount, came the powerful concept of the Peace of God. It was the work of scholars, the work of cautious scholars. As that incomparable historian Frederick W. Maitland explains it: "The cautious particularity of the canons, resolutions, oaths, their provisos and exceptions and saving clauses . . . are the very essence of the story. Those who strive for peace are in the end successful, because they are content with small successes and will proceed from particular to particular, placing now the *villanus* and now the *femina nobilis*, now the sheep and now the olive tree, now the Saturday and now the Thursday outside the sphere of blood-feud and private war. When they are in a hurry they fail, for they are contending with mighty forces."

Not until the 13th century in France was the right of private warfare, on the comparatively small front of the Peace of God, destroyed: it was a gradual, snail-like process all the way, through three long and bloody centuries. We too must be content with a progression of small successes.

I have been, perhaps, over-long and over-technical in making this point but, at any rate, I hope it now is clear that in our search for peace we too shall fail when we are in a hurry; for we too are contending with mighty forces.

In the Middle Ages the church might, and did, proclaim the concept of the brotherhood of man as the logical corollary of the fatherhood of God; but the concept could not be made good. And the reason it could not be made good was that it was proclaimed in a society where, by and large, a man stayed where he was, in place and in station, in a minutely graded hierarchy in the social structure. It was, in short, a society in which status governed both what you did and what you were. By and large it was the land you held, or the land you tilled under another's holding, which determined your status. There was no more land to distribute, and hence, in that society, no way to break status.

This is, I realize, much too cavalier an account of a situation that has engaged the attention of scholars for hundreds of years; but my canvas is

small compared to my subject and I believe my painting to be substantially true to the subject.

It was the distinctive contribution of the New World to break the lock-step of status.

One example will make this clear.

The Dutch West India Company, true to the traditions of the Middle Ages, in 1629 granted to Kiliaen Van Rensselaer, a merchant of Amsterdam, a patroonship up the North River at what is now Albany, New York.

It was the intent of their High Mightinesses, the States-General of the United Netherlands, to set up in the New Netherlands, by their grants of large landholdings, a replica of their European feudal society, based on status, which in turn was based on the ownership of that land. The tillers of that soil were not to own the soil: the privileges and exemptions of the European feudal lord were to be transplanted to the New World.

Such was the plan, the European plan, formed in the council rooms of Amsterdam; and in pursuance of his part of it Van Rensselaer sent Wolphert Gerritse Van Kouwenhoven as one of his agents to the New Netherlands, to acquire such title as might be had from the Indians and to establish Dutch settlers, without ownership, on his land.

It did not take Van Kouwenhoven long, after he had fulfilled his duties to his principal, to figure out that if he could acquire land for Van Rensselaer, he could also acquire it for himself. And that is exactly what he did, in 1636 on Long Island to be exact; and then he did the even more revolutionary thing of selling portions of his land—giving ownership of it—to his friends and neighbors from his native Amersfoort in Holland. And what Van Kouwenhoven did, thousands of others did—with the result that every man in America either became, or had the chance here to become, as good as the next; and the lock step of Old World status found no home in the New.

But again we are mistaken if we think of this as a sudden thing. The bloody Rent Wars of the Hudson Valley are a measure of the continuing power of the Old World feudal concepts through a century and a half. And it was not until the West, beyond the Alleghenies, was opened to settlers who could own their land that the shackles of status were completely broken in the New World.

Robert B. Warren has explained the consequences of this: "Only with the elimination of status from the conceptual structure of human society, could the way be cleared for the spiritual ideal of the brotherhood of man. This was the New World's contribution to civilization. It was not the gift of philosophers or statesmen or conquerors. It was not even the gift of the theologians. It was the gift of the New World itself, to itself, and to Europe."

Thus it was that Michel-Guillaume de Crevecoeur, writing in 1782, from Upper New York State could say, "This great metamorphosis has a double effect upon the settler; it extinguishes all his European prejudices; he forgets

that mechanism of subordination, that servility of disposition which poverty had taught him. . . . If he is a good man, he forms schemes of future prosperity; he proposes to educate his children better than he has been educated himself; he thinks of future modes of conduct, feels an ardour to labour he never felt before. Pride steps in, and leads him to everything that the laws do not forbid: he respects them; with a heart-felt gratitude, he looks toward that government from whose wisdom all his new felicity is derived, and under whose wings and protection he now lives. These reflexions constitute him the good man and the good subject.

"Ye poor Europeans, ye, who sweat and work for the great—ye, who are obliged to give so many sheaves to the church, so many to your lords, so many to your government, and have hardly any left for yourselves—ye, who are held in less estimation than favourite hunters or useless lap-dogs—ye, who only breathe the air of nature because it cannot be withheld from you; it is here that ye can conceive the possibility of those feelings I have been describing; it is here the laws of naturalization invite every one to partake of our great labours and felicity, to till unrented, untaxed lands!"

But as de Crevecoeur saw the vision, he moved too fast in his conclusions. It was not to be so easy, so fast, nor so sure.

"The progress of society," wrote Sir Henry Maine in one of the most brilliant of legal generalizations, "is from status to contract." The essence of contract is that one makes a choice of what one will or will not do. The greater the range of choice, the greater the rate of change: for change is dependent upon the possibilities that individual men see for the future. It is so in your medical researches: it is so in all human affairs.

Thus it is that since the discovery of America the rate of change, in both the Old World and the New, has quickened beyond any previous manifestations. And thus it is also that the concept of the brotherhood of man need not be dreamed in vain.

If there is anything that we—those of us who carry on researches and those of us who run foundations—anything that we should have learned, it is that no one can say from what direction, from what beginnings, great advances will come. We can, perhaps, predict the next step in a progression of steps: we cannot predict the new path leading from our little clearing, through the wilderness of the future, to the heights of the good life we want to scale, and which, being Americans, we know we can and shall scale.

But I must move my statement toward its conclusion. What I am saying is that just as no one could predict Hiroshima from Einstein's formula of 1905 and just as the methods of the WCTU may become outmoded by the work of biochemists, so also anything can happen in any field at any time —upon one condition.

That condition is, and it is a peculiarly American condition, that we give all men a chance for as much education as they can take, that they have freedom of choice as to what they will do with their education, as to the direction

their education will take, and to carry on their work after they are trained to do it.

This is not, you see, a simple condition: it may not be one, but several conditions.

Reasonably, you will ask me to justify the statement. What am I really saying? Of course I am saying that we must provide a very large number of highly trained, utterly competent persons to keep the machine of civilization in working order. We need a larger proportion of the population trained to levels of high technical competence than we ever needed before.

But I am saying also that we need a great deal more. I am saying that we cannot afford to miss any of the very rare persons who pioneer the future. I am saying that suppose George Shull, who developed hybrid corn, had remained on the family farm in Ohio instead of being trained as a geneticist, what would the millions of Europe be eating now? You might say that they would never have been born. But that would not be true because commercial hybrid corn is only about 15 years old. Suppose Thomas Jefferson had been born poor, unable to get to the College of William and Mary, unable to buy books and to afford time to think and learn. Suppose James Madison had never had a chance to study at Princeton. What would our past have been, what would our future be? These are, I submit, real questions: there are no greater questions for you and me.

I am saying, further, that all of our science and medicine and all of our technology, while not negligible in any fundamental view of us, are not to be compared in influence with the Sermon on the Mount, the Ten Commandments, the Declaration of Independence, the Constitution of the United States. It is such creative efforts of the mind and spirit, somehow diffused into our minds and spirits, which make us what we are, free men with free ideas.

Christ speaking the Sermon on the Mount, Copernicus shaking men's minds free from the theories of a fixed earth, Thomas Jefferson writing the Declaration of Independence, Leonardo da Vinci painting the Last Supper, Newton understanding the laws of motion, Bach composing, Shakespeare creating Hamlet—these are what have made us what we are—not the radio, the telephone, the motor car, nor any of our technology. All our hospitals and all our healing devices and methods can compare with one of these in importance only as expressions of the brotherhood of man.

You may now be saying to yourself: this fellow aims high, too high. We are working men, not stargazers. Where does he expect these great human beings to come from?

The answer is that I don't know. My conclusion is modest and it is this: unless we give them a chance to come they will not come. Let us give them the chance.

Thus it is that I could not approve a Selective Service Law which makes provision for assuring a supply of leaders for science and technology, medicine and agriculture and industry and for nothing else. Thus I could not

approve a National Science Foundation syphoning off, by the power of allocating funds, into science and technology more than its proportionate share of the nation's ability. Thus I could not approve of any foundations deciding that this or that field is the field most necessary to advance to the exclusion of other fields and kinds of training. I could not approve, because nobody knows what is most important, and nobody can know until somebody goes ahead and does it. I am simply saying that somebody must recognize on a sufficient scale that the future will need more than science and engineering, more than medicine and food; that the needs for those who will state and provide for the higher values of American life, the values for which we always have fought, are at least as essential as the means to fight for them.

And if you want me to "go practical" with you as a final part of my statement, I will do so:

President Roosevelt during the war asked a series of four questions to the end that the lessons of war might, as the President said, "be used in the days of peace ahead for the improvement of the national health, the creation of new enterprises bringing new jobs and the betterment of the national standard of living."

The President's deep concern for this question is shown in the concluding sentences of his letter to Dr. Vannevar Bush: "New frontiers of the mind are before us, and if they are pioneered with the same vision, boldness, and drive with which we have waged the war we can create a fuller and more fruitful life."

Of the answers given to these questions, the answers as respects science and technology have been listened to, but those who pleaded for a proportional share, a modest share, for the humanities and social sciences have not been heeded.

Yet the answer to those who insist upon science and technology, if they insist upon science and technology and nothing else, *as some do,* is plain; and it goes like this, as a very practical matter: Science, like anything else paid for out of the public's purse, is justifiable only in so far as it results, as a long-term proposition, in a fuller and more fruitful life to the people at large—by the improvement of standards and satisfactions of living, by the creation of new enterprises, bringing in new jobs. But these results—such as improvement of our standards and satisfaction of living and the creation of new enterprises—are not merely matters for science. They are also in very important ways matters of economic organization, of systems of taxation, of fair public administration, of resistance to pressure groups, of the understanding of our heritage and of each other, of love of country and of many other factors. To state the matter quite simply and practically, we shall not get the benefits of science in the best manner in our national life unless really good and all-around studies are developed in connection with many broad economic, social and political questions in our national organization, unless there be understanding of the forces that have made us what we are. To get those studies and this understanding, we need to develop

social thinkers—more of them and better ones than we now have. And not only do we as a nation need them, but the world also needs them; and science, as socially useful science, needs them. For without those studies and without this understanding, free science is going to be something future scientists may read about but will not have. Again as a practical matter, the plain truth is that, as we increase the tempo of scientific advance, the more we shall need to better the quality of thought and understanding over the whole spectrum of the human mind and spirit.

But you will have gathered that I am not primarily talking only about matters ordinarily considered within the range of practicality. I have been trying to say that in this present world of power, more power will not do for the long haul. It may serve for the short term, fighting the holding actions which may be needed at the moment—and let us pray that it will serve—but for the long term the use of power is self-defeating for the life we would consider worthy of the vision of America. Somewhere, sometime, must come men who will break through the encrustations of time and place and tradition and motive, of ignorance and greed and self-interest—who will bring the brotherhood of man appreciably closer.

They will not, they cannot, come unless, in Thomas Jefferson's saying, "worth and genius are sought out from every condition of life and completely prepared by education for defeating the competition of wealth and birth." This was a great 18th century problem. Nor will they, can they, come if the prevailing thought of the 20th century is that "civilization can be bred to greatness and splendor by science alone." If those efforts of the mind and spirit that yield results comparatively fast, if the activities that are deemed useful for present progress and power and strength are exalted and entrenched, and if those activities which determine the character of people are denigrated, then, as a long term proposition, the structure of freedom, the structure of liberty and order under justice, of every life, will fade. We can live for a time on our moral and spiritual capital; but, like all capital, this capital disappears if not renewed.

There are signs that this is a great 20th century problem.

I agree with Raymond B. Fosdick, the recent president of the Rockefeller Foundation, when he said: "Certainly in our search for the means to control our own fate we must not overlook the possibility that the universality of mankind may be achieved by art or music, a poem or song, perhaps more effectively and lastingly than by engineering, medicine or economics."

Nor will these, can these, path-breaking minds, these renewers of moral and spiritual capital, come and develop and state our values unless we maintain in America the climate of the mind and spirit that makes this place the world's stronghold of the rights that we sum up as freedom: that sum is the essence of our strength—our internal and external strength, for both the long and the short term. This is, as Elihu Root once said, the supreme treasure of our country.

I expressed the hope, in the beginning, that in these reflections of mine your minds and hearts would find some validity for your thinking. If so, I now shall say to The Doctor as Citizen—conscious of history and with a concern for the future—that there are no men better placed, no minds better fitted, to make the sense of these reflections effective for the long haul. I am not in a hurry: we too are contending with mighty forces and if we are in a hurry we shall fail. We too must be content with a progression of small successes—the successes that come through the cautious particularity, in Maitland's phrase, of those who have the vision of freedom and who know their business.

CASE REPORTS

THE EFFECT OF PITUITARY ADRENOCORTICOTROPIN (ACTH) IN DERMATOMYOSITIS *

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Since the report that an adrenal cortical hormone induces clinical improvement in the symptoms of rheumatoid arthritis,[1] it has been suggested that other diseases with extensive involvement of collagen tissue might be similarly benefited. A supply of adrenocorticotropin (ACTH-Armour †) was made available to us for study in dermatomyositis and two patients have been treated. One patient who suffered also from advanced carcinomatosis received no apparent benefit from 12 days of treatment, but the effect on the other patient was dramatic. Improvement began within a few hours after the first dose, and the patient was transformed from a critical state into one of good health within a few weeks. He was kept on treatment for 53 days and has not had a relapse during a period of four months since the administration of the hormone was discontinued. He showed definite evidence of adrenal cortical stimulation and some manifestations of hyperfunction. The over-all effect has been so striking that we feel this early report is advisable.

A white male executive, aged 30, was admitted to the New York Hospital on July 6, 1949, because of pain in the left side of the neck, and pain and soreness in the muscles of the right leg. Forty-eight hours prior to admission he first noted a feeling of fullness in the left side of the neck associated with some aching and tenderness of this area. Because of persistence of these symptoms and a low grade fever, he saw his physician the following morning and was given 300,000 units of penicillin. The pain gradually became more severe and he was soon unable to swallow. That afternoon the muscles of his right leg became sore and painful and the next day, e.g. the day of his admission, he noted a tender area over the right triceps muscle and another at the base of the spine.

Seven years previously, in 1942, the patient had a similar illness, characterized by sore throat, fever, and muscle pain, which at first was mild, but soon became excruciating. He was admitted to the Hospital of the Rockefeller Institute. A few days after his admission, he was transferred to the surgical service of the New York Hospital because of marked respiratory distress occasioned by swelling of the neck and by edema of the pharynx. His temperature was 39° C., the pulse rate was 120 per minute, and the blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. He had considerable respiratory distress and appeared acutely and seriously ill. There

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† The authors are indebted to John R. Mote, M.D., Medical Director, the Armour Laboratories, Chicago, Illinois, for the ACTH used in these studies.

were marked swelling of the soft tissues about the head, and swelling, redness, induration, and tenderness of the left side of the neck, left scrotum, left forearm, and left foot. Examination of the urine revealed a 3 plus albuminuria. Examination of the blood showed a hemoglobin concentration of 12.1 gm. per 100 c.c., 4 million red blood cells per cu. mm., and 16,500 white blood cells per cu. mm., of which 85 per cent were mature polymorphonuclears, 1 per cent metamyelocytes, 1 per cent eosinophiles, 8 per cent lymphocytes, and 5 per cent monocytes. The patient was believed to have widespread cellulitis. However, surgical exploration of the neck revealed no purulent process. Microscopic examination of tissue removed at operation was reported as "fatty tissue showing mild inflammation." A few days later, a tracheotomy was performed because of increasing dyspnea and cyanosis. During the time he was in the New York Hospital his temperature varied between 39° and 40°. New areas of swelling and induration appeared and muscular pain was severe and unremitting. He was periodically irrational and was incontinent of urine and feces.

A B C

FIG. 1. Effect of ACTH. *A*. The day before ACTH. Note swelling of neck and parietal regions. The head was immobilized by pain. *B*. Seventy-two hours after treatment with ACTH was begun. Note diminution of swelling. *C*. After 47 days' treatment with ACTH. Note suggestion of "moon-faced" appearance. The edema of dermatomyositis is absent.

The white blood cell count increased to 38,000 per cu. mm. two weeks after his admission. He was treated with sulfanilamide, sulfadiazine, and small blood transfusions. The level of hemoglobin and red blood cell count increased, but there were no other signs of improvement. After 21 days in the New York Hospital the edema about the neck had subsided so that he no longer needed surgical care and he was returned to the Hospital of Rockefeller Institute.

He remained in the Hospital of the Rockefeller Institute for five and one-half months and during this time he lost 67 lbs. However, gradual improvement occurred toward the latter part of his period of hospitalization. At the time of his discharge he was quite well except for flexion contractures of the ring and fifth fingers bilaterally due to prolonged immobilization of his hands in this position. Microscopic examination of a portion of muscle removed during his illness revealed loss of structure of the fibers, hyperchromatic nuclei, and periarteriolar collections of small lymphocytes. Hyalinization of the connective tissue, edema and hemorrhage were noted. These changes were considered to be characteristic of dermatomyositis.

He remained entirely well from 1942 until the onset of the present illness and served in the armed forces overseas for several years. His past history was im-

portant otherwise only for bouts of hay fever in the spring and fall since childhood and for mild asthma since puberty. The family history was irrelevant.

When he was admitted to the New York Hospital in 1949, his rectal temperature was 39° C.; the pulse rate was 104 per minute; the respiratory was 20 per minute; and the blood pressure was 135/80. The patient was a husky, well built young man who appeared acutely ill and had pain with every movement. The entire left side of the neck was markedly swollen and exquisitely tender; soft non-pitting edema overlay a deep, fixed induration. There was edema of the left side of the uvula. Examination of the heart revealed no abnormalities except the rapid rate. Throughout both lung fields a few wheezes and coarse rhonchi were heard. Both calves, the anterior thighs, and the right triceps area were tender on palpation. In these areas there were redness and localized swelling. The deep reflexes were normal throughout.

Examination of the urine revealed 1 plus albuminuria; examination of the blood showed a hemoglobin level of 15 gm., 4.7 million red blood cells, and 12,000 white

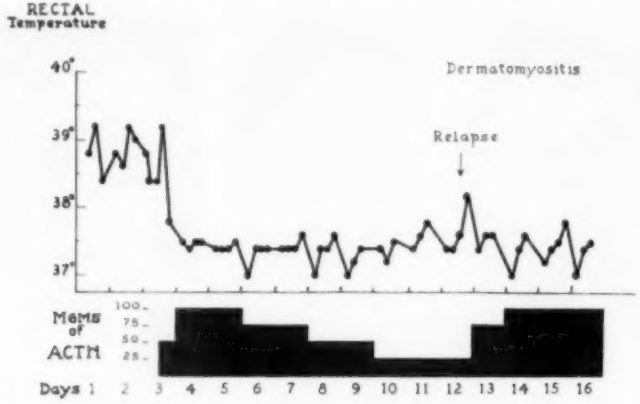

FIG. 2. Effect of ACTH on the temperature course.

blood cells of which 80 per cent were adult polymorphonuclear leukocytes, 7 per cent were band forms, and 1 per cent were eosinophiles. The sedimentation rate was 51 mm. per hour (Wintrobe). The concentration of blood urea nitrogen was 21 mg. per cent, and that of total protein was 7.1 gm. per 100 c.c., of which 4.9 gm. were albumin and 2.2 gm. were globulin. The fasting blood sugar level was 93 mg. per cent, the level of potassium in the serum was 4.3 m.eq. per liter, that of sodium 143 m.eq. per liter, and that of chloride 86 m.eq. per liter. The trichinella precipitin test was strongly positive in a dilution of 1:640. The electrocardiogram was essentially normal. His weight was 156 lbs.

Shortly after his admission to the hospital, the rectal temperature rose to 40°, and the pulse rate ranged between 120 and 130 per minute. He developed new lesions over the arms, neck, legs, and later over the abdomen. The muscular pain progressed so that all the muscles of the extremities, and later the abdominal muscles, were involved. He had transient episodes of severe chest pain, first on the right and then on the left side. The pain lasted for two or three days and required infiltration of certain intercostal nerves with procaine for relief. There was a transient friction rub with pleuritic pain over the left lower lung field. The pain in the extremities became so severe that it was necessary to administer 150 mg. demerol nearly every

four hours. During the first month that he was in the hospital he lost 29 pounds and there was marked muscular wasting. His course continued to be stormy.

On August 4, the day before ACTH was started, the patient had pain in the neck, arms, calves, and thighs. Two intercostal nerve blocks were done four hours apart because of lancinating pain in the areas of distribution of T 6, 7, and 8. There was marked swelling of the head, neck (see figure 1) and arms, and there were erythematous, slightly tender skin and subcutaneous lesions over the neck and arms. His temperature and pulse rate were high (figure 2). Examination of the blood showed a total of 64,000 white blood cells per cu. mm., of which 60 per cent were adult polymorphonuclears, 27 per cent band forms, 3 per cent metamyelocytes, 3 per cent myelocytes and 1 per cent promyelocytes. The eosinophile count was 80 per cu. mm.; following the subcutaneous administration of 0.5 mg. epinephrine, the eosinophile

TABLE I

Blood Changes Following Administration of ACTH

Day of ACTH	Serum Na	Serum K	Fasting Blood Sugar	Hb.	R.B.C.	W.B.C.	Eosinophiles
	m. eq. per liter	m. eq. per liter	mg. per 100 c.c.	gm.	millions	thousands	per cu. mm.
0		5.0	93	10.3	3.3	64.1	81 (61*)
2			86				25
4			63	9.3	3.1	30.5	31
5	143	4.3	69				31
6			65				25
7			59				18
8			83	11.0	3.7	20.5	31
9			64				
10			75				35
13	141	4.5	89				25
15			108				28
19			66	11.5	4.0	15.0	24
21	136	3.8					
22			69				12
26				11.6	4.1	13.3	12
27	140	3.1	79				
29			65				18
60							61**

* 1 hr. after 0.5 c.c. adrenalin solution 1:1000.
** 8 days after ACTH had been discontinued.

count was 61 per cu. mm. The urinary excretion of creatine was 2.04 gm. during 24 hours. The patient was given the regular hospital diet.

On the following day (August 5) the administration of ACTH in doses of 25 mg. every six hours was started. Within six hours after the first dose had been given, at 2 p.m., the temperature fell from 39.2° to 37.8°, the lowest temperature in two weeks. Ten hours after therapy was started, the patient noted considerable diminution in the severity of his pain and thereafter required no further demerol. By the next morning he could move and lift his legs without pain for the first time since onset of his present recurrence of the disease. He could pronate and supinate the arms with a minimum of pain and could turn the head about 25 degrees to either side. No movement of the head had been possible before ACTH was given. There were distinct reduction of the swelling about the face, neck, and arms and disappearance of tenderness of the skin lesions (figure 1). On the evening of August 6, he had some pain in the left chest but this lasted for only a few minutes. From this time on he continued to improve rapidly with disappearance of edema, skin lesions, and pain. His temperature remained normal. The level of white blood cells which had been 64,100

before treatment, fell steadily to 13,300 with a gradual diminution in the number of immature leukocytes in the peripheral blood. The urinary excretion of creatine dropped dramatically. The eosinophile count varied between 12 and 31 per cu. mm. during the course of treatment. The temperature chart and the daily dosage schedule of ACTH are shown in figure 2.

When the daily dose of ACTH was reduced to 25 mg. (on the seventh day), the patient again experienced pain in the legs. The pain increased in severity during the next 24 hours but disappeared promptly when the dosage schedule of 25 mg. of ACTH every six hours was resumed. The dose was then gradually reduced by from 5 to 15 mg. at a time until the drug was discontinued entirely after having been given over a period of 53 days. The total amount of ACTH administered was 3.965 gm. There was a mild relapse when the dose was reduced to 60 mg. on the thirtieth day, but almost no evidence of relapse after therapy was abruptly ended.

During treatment there were no clinical signs of hypopotassemia, although the concentration of potassium in the serum fell to 3.1 m.eq. per liter. Serial electrocardiograms were normal. Other laboratory findings are listed in tables 1 and 2.

TABLE II

Urinary Changes Following Administration of ACTH

Daily Urinary Output

Day of ACTH	17-Ketosteroids	Preformed Creatinine	Creatine
	mg.	gm.	gm.
0	5.55	1.033	2.041
1			0.867
2	8.15	0.934	0.919
3			0.639
5			0.411
6	9.15	0.809	0.241
8	5.80	0.793	0.256
11	12.8	1.410	0.240
12	22.1	1.229	0.205
14	24.8	1.336	

The patient gained 33 pounds from the time ACTH was started until his discharge from the hospital 30 days later.

DISCUSSION

The ACTH used was prepared by the Armour Laboratories and is similar to the material previously used and extensively studied at the Peter Bent Brigham Hospital by Thorn and his associates.[2] It is prepared from hog pituitary glands and is a relatively pure substance. It has a small amount of oxytocic activity but is free from significant amounts of pituitary growth promoting, gonadotropic or thyrotropic actions. The effects in subjects with normal adrenal glands suggest that ACTH stimulates the production of most of the active agents elaborated by the adrenal cortex.

In our case, the eosinophile counts were determined daily during the period of treatment and representative ones are listed in table 1. There was a prompt fall which was much greater than 50 per cent, and the count remained low throughout the course of treatment. Eight days after the last dose of ACTH, the eosinophiles had increased almost to their pre-treatment level. These findings indicate a good adrenal cortical response.[3] Further evidence of adrenal

cortical stimulation is shown by the five-fold increase in the urinary output of 17-ketosteroids (table 2). The concentrations of sugar, sodium and potassium in the blood are listed in table 1. These data show a slight fall in the level of blood sugar instead of the rise one might have expected, and a slight decrease in the level of potassium in the serum. The latter change never was associated with any muscular weakness or with alteration in the T waves of the electrocardiogram.

There were other changes in laboratory data during the course of treatment that appear to have been related to the improvement in the clinical status of the patient rather than to any direct or specific action of the hormone. The most striking of these was the fall in the output of creatine from a previously very high level. The creatinine output was not altered. The urinary creatine and creatinine values are shown in table 2. The fall in creatine output occurred when signs of inflammation in the muscles were subsiding rapidly, and probably furnishes a good index of the amount of improvement in the functional capacity of the muscles and of the increased ability of the muscles to retain creatine. Other changes, apparently due to improvement in the clinical state of the patient, were the correction of an anemia without the use of either iron or liver therapy, and a fall in the white blood cell count from a very high level to a level that was almost normal (table 1). The later change is of especial interest since ACTH may increase the number of polymorphonuclear leukocytes in normal subjects.

The patient received a total of 3.965 gm. ACTH during the period of 53 days he was under treatment. We naturally were interested to see if hyperadrenalism would develop, and signs of this state were watched for carefully since the patient showed evidence of good adrenal cortical stimulation and was given ACTH for a long period of time. However, the manifestations of hyperadrenalism never were marked but probably were sufficient to indicate that the condition existed. His beard and body hair grew more rapidly than before, but though he had previously had a fairly heavy beard, he did not have to shave more than once a day. Evaluation of his body fat was made difficult by an improvement in his general nutritional state. There was a slight change in the contour of his thighs toward a feminine type. His face became rounded and his family considered him "moon-faced" even before possibility of this change had been mentioned to them. The series of photographs in figure 1 shows this rounding of the face. His libido was perhaps less than is usual for the average convalescent patient of his age, and specimens of his semen contained abnormally low numbers of spermatozoa.* However, these findings may not be significant since spermatozoa had been observed to be scant during the year subsequent to his first attack of dermatomyositis, and long before he ever had received ACTH. His testicular function may have been altered by the widespread disturbance of collagen tissue during his first attack. Throughout the course of treatment, the patient's blood pressure remained normal.

In considering the clinical apects of the case and the response to ACTH, it should be emphasized that we were dealing with a very acute form of dermatomyositis. This is indicated by the severity of the first attack, the long and complete remission, and the rapid development of the second attack. It is shown also by the high fever and the marked prostration, the hyperleukocytosis, and

* There were nine spermatozoa, only one of which was motile, per high power field; three months later there were 300 spermatozoa, 200 of which were motile. The counts were made by Dr. R. S. Hotchkiss.

the widespread involvement of collagen tissues. There was excruciating spontaneous pain; and the skin and the subcutaneous and muscular lesions were all tender, and the mucous and serous membranes also were involved. He was seriously ill throughout the first part of his second attack, and especially so during the week before ACTH therapy was started.

The response to treatment was dramatic and began within six hours after the first dose of 25 mg. of the drug. He received this amount every six hours for the first 48 hours, and then the dose was reduced to three injections a day. Every two days after this, the dose was reduced by 25 mg. so that on the seventh and eighth days after treatment had been started, he was getting only 25 mg. per day. This amount was insufficient and his symptoms recurred to such a degree that full dosage of 100 mg. a day was reinstituted. The symptoms then promptly subsided and the dosage was slowly reduced, at intervals of five days, until on the fifty-third day the drug was stopped entirely.

SUMMARY

A detailed report is made of a case of acute and severe dermatomyositis in a young adult male who was treated with ACTH. Good evidence of adrenal cortical stimulation was observed and the patient made a very dramatic recovery. After a course of treatment of 53 days, during which he received nearly 4 gm. of the hormone, he remained well without further treatment. Only mild manifestations of hyperadrenalism developed.

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SEVERE ACIDOSIS DUE TO PHENOL POISONING: REPORT OF TWO CASES*

By IVAN L. BENNETT, JR., M.D., DAVID F. JAMES, M.D., and ABNER GOLDEN, M.D., *Atlanta, Georgia*

IN view of the fact that acidosis in phenol poisoning has received little attention in the literature, and because of the therapeutic importance of reversing this condition, report of such cases seems indicated. We have recently observed two patients with phenol poisoning in whom the most prominent systemic mani-

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festation was acidosis and in whom a dramatic response was obtained with intravenous sodium bicarbonate.

Case Reports

Case 1. A 50 year old morphine addict was admitted to Grady Hospital on February 14, 1947, at 2:00 a.m., approximately 45 minutes after swallowing 2 ounces of liquefied phenol (88 per cent) with suicidal intent.

On admission he was stuporous, his skin was cold and clammy, pulse was rapid and weak and the systolic blood pressure was 90 mm. of mercury by palpation. Respirations were stertorous and his breath smelled strongly of phenol. Gastric lavage with 500 ml. of olive oil was performed immediately and he was given saline and plasma intravenously. Though his blood pressure rose to 120 mm. of mercury systolic and 90 mm. diastolic, he remained stuporous and unresponsive. Laryngoscopic examination revealed burns about the hypopharynx without obstruction. The gastric washings contained gross blood.

The pupils were constricted and did not react to light. The skin was covered by bluish needle marks, many of which followed the course of the superficial veins. Respirations continued to be deep and the rate was 36 to 40 per minute. Coarse râles were heard in the lungs. An electrocardiogram on admission showed auricular flutter with varying auriculo-ventricular block. Lumbar puncture revealed normal spinal fluid.

At 11:00 a.m., nine hours after admission, because of continued Kussmaul breathing, the plasma carbon dioxide combining power was determined and found to be 19.9 volumes per cent. He was given 28 gm. of sodium bicarbonate intravenously as a 3 per cent solution which caused a rise in carbon dioxide combining power to 41.1 volumes per cent at 4:00 p.m. This was accompanied by a dramatic clinical improvement. The hyperpnea ceased, the patient became rational, responsive, and was able to converse. During the next 24 hours, he received an additional 32 gm. of sodium bicarbonate by stomach tube and the carbon dioxide combining power rose to 49.0 volumes per cent.

The first urine obtained was green in color, but changed to dark brown on standing. Reaction was acid. There was no albumin in the first specimen, but 12 hours later there was marked albuminuria and cylindruria. There was never a significant oliguria. Albuminuria persisted for 10 days, but cleared completely before discharge.

Except for nausea, vomiting, and diarrhea during the first week, the patient improved steadily and was discharged on the twentieth hospital day. The blood nonprotein nitrogen never rose above normal levels and liver function tests revealed no evidence of residual damage. The electrocardiogram returned to normal and the plasma carbon dioxide combining power on the ninth day was 57 volumes per cent.

The patient said that he had taken 0.5 grain of morphine intravenously before ingesting the phenol. This probably accounted for the constriction of his pupils on admission.

Case 2. A 19 year old white housewife was admitted to Grady Hospital on May 28, 1947, at 1:30 p.m., one and one-half hours following ingestion of about 15 c.c. of liquefied phenol with suicidal intent. She was conscious and rational at the time of admission, complaining of severe nausea and burning in the throat and epigastrium. Stomach lavage with olive oil was performed and she was given saline intravenously. Laryngoscopic examination showed superficial burns and slight edema of the hypopharynx.

Blood pressure on admission was 104 mm. of mercury systolic and 70 mm. diastolic, and pulse rate was 88. Except for marked epigastric tenderness and several scars on the left wrist (the results of a previous suicide attempt), physical examination was normal.

The patient's nausea continued, and one hour after admission she began to vomit almost pure blood. She began to have diarrhea, passing copious amounts of dark red blood with clots. She gradually became cyanotic and stuporous. Blood pressure dropped to 70 mm. of mercury systolic (diastolic unobtainable) and the extremities became cold. The administration of nasal oxygen and 1200 ml. of whole blood were without effect on the blood pressure, cyanosis, or stupor.

At 4:30 p.m., three hours after admission, the plasma carbon dioxide combining power was 22.6 volumes per cent. At that time her respirations were not characteristic of acidosis. Following the administration of 30 gm. of sodium bicarbonate intravenously, she improved markedly, becoming conscious and able to converse. At 8:00 p.m. the carbon dioxide combining power had risen to 41.2 volumes per cent. At that time the cyanosis had disappeared, and she appeared much improved though she continued to have spells of severe nausea with hematemesis. At 11:30 p.m. the patient again became stuporous and cyanotic, and at this time her respirations were of the Kussmaul type. Carbon dioxide combining power was found to have dropped again to 28.5 volumes per cent. Another dose of 30 gm. of sodium bicarbonate was given by vein, and 30 gm. were given by stomach tube. She rallied once more, cyanosis lessened, and she conversed rationally. Improvement was brief, however, and she again lapsed into coma, with cyanosis and hyperpnea. Despite an additional 30 gm. of sodium bicarbonate intravenously (total amount, 120 gm.), she died 16 hours after admission. The plasma carbon dioxide combining power 15 minutes before death was 21.5 volumes per cent. Her total urinary output was only 75 ml. This was almost black and contained many red cells and casts and 4-plus albumin. An electrocardiogram taken shortly after admission showed high T waves and prolongation of the Q–T interval. There was no spreading of the QRS complexes. Autopsy permission was not granted.

Discussion

The local effects of ingested phenol include severe burns of the mucous membranes of the mouth and pharynx and necrosis of the gastrointestinal mucosa sometimes with extensive hemorrhage. These are due to the necrotizing action of this poison. Current texts of pharmacology and toxicology all give remarkably similar descriptions of the systemic effects of phenol. These include muscular weakness and occasional tremors or convulsions, rapid depression of respiration, circulatory collapse, coma and death. This course of events has been ascribed to direct action of phenol on the central nervous system. In addition, acute tubular necrosis with oliguria or anuria is said to occur frequently.

The occurrence of acidosis in phenol poisoning has received very little attention. Clarke and Brown [1] in their report of 13 cases of phenol poisoning mention increased depth and rate of respiration in five instances. They did not ascribe these symptoms to any cause. Gibbs [2] in outlining the treatment of phenol poisoning advocated the parenteral administration of at least 20 gm. of sodium bicarbonate within the first 24 hours, without discussing its rationale. The only mention of acidosis as such in the American literature, is the suggestion of Bastedo [3] that "sodium bicarbonate may be given to combat acidosis."

In view of the striking symptomatic response of our patients to alleviation of acidosis by intravenous sodium bicarbonate therapy, it appears probable that many of the systemic effects of phenol may be due to the acidosis. This does not imply that other effects are unimportant. The mechanism by which phenol produces acidosis is unknown. Røe [4] has recently suggested that the acidosis caused by

methanol poisoning is due to interference with enzyme systems controlling cellular respiration. It is possible that phenol may have some similar action.

SUMMARY

Two cases of acute phenol poisoning are described, in which a predominant systemic manifestation was acidosis. Marked symptomatic relief was obtained by vigorous intravenous sodium bicarbonate therapy.

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CYSTIC TUMOR OF THE THYMIC REGION AND MYASTHENIA GRAVIS: REPORT OF A CASE IN WHICH THE TUMOR WAS REMOVED *

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REMOVAL of a tumor of the thymic region to influence the course of associated myasthenia gravis was first done in this country by Blalock [5] in 1936. Since that time there have been numerous reports of this procedure.[7, 11, 14, 15, 16, 18] More recently the surgical attack has been expanded to include cases of myasthenia gravis in which no thymic tumor can be demonstrated. These have been subjected to exploration of the anterior mediastinum and excision of all recognizable thymic tissue.[3, 4, 9, 17]

Results of these operations and other studies seem to indicate the following relationships of the thymus gland and its tumors to myasthenia gravis.

1. Demonstrable pathology of the thymus occurs in at least 50 per cent of the cases of myasthenia gravis which come to autopsy.[1]

2. The thymus is not the only ductless gland which may influence the pathogenesis of myasthenia gravis. The thyroid and adrenals and even pregnancy have been shown in some cases to have a relationship to the course of the disease.[8]

3. Myasthenia gravis has been produced in dogs by repeated grafting of young thymus tissue and by the infusion of thymic extracts.[1] In humans, the removal of thymic tumors, even the extirpation of all thymic tissue, does not result in cure of the disease.

4. In some instances rapid and prolonged remissions of myasthenia gravis have followed the removal of thymic tumors or total thymectomy.[3, 5] Those patients from whom thymic tumors are removed do no better than those without tumors from whom the entire gland is removed.[17]

5. Surgery of the thymus gland does not uniformly produce remissions of

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myasthenia gravis. Study of postoperative results suggests that the best chances of recovery are to be expected in patients who have not had the disease for an extended period. It is possible that prolonged disease results in irreversible changes.[8]

6. Primary tumors of the thymus gland coming to operation or autopsy are found to be associated with myasthenia gravis in almost 100 per cent of cases. These tumors lie in the thymic region and are attached to the pericardium. They may be encapsulated, may be solid, and may show histologic patterns denoting the thymic origin. They may be degenerated or cystic and filled with precipitated amorphous material, there being no histologic pattern to denote the origin. Such degeneration and cyst formation have been encountered in both the presence and the absence of previous roentgen-ray therapy to the tumor. Primary thymus tumors may be invasive, infiltrating the contiguous structures. Metastases may occur but are seldom found below the level of the diaphragm. Prognosis in regard to associated myasthenia gravis cannot be made from the histologic picture.[12]

Case Report

A white male, farmer, age 56, walked into the office on August 22, 1946. He was able to speak in a weak and indistinct whisper. He was unwilling to talk because all efforts at speech produced nausea. Relatives who accompanied him stated that he had been in bed because of a cold for the previous three days. There had been little fever and slight cough. He had complained of "a choking feeling" in his chest and had shown progressive difficulty in speaking, chewing, and swallowing. For several months he had been having "spells" in which "his chin would draw down on his chest." It had been noted that these "spells" followed and were dependent on hard work.

His face was expressionless, and he was moderately dyspneic with some tendency to stridor. This, with the history of speech, chewing, and swallowing difficulties, and the previous history of inability to hold up his head when tired, aroused the clinical suspicion of myasthenia gravis.

Because of the possibility of an associated thymic tumor an immediate fluoroscopic examination of the chest was made. A dense anterior mediastinal shadow seen in all positions was best visualized in the lateral view. In this projection the shadow was roughly circular, of uniform density, and was located anterior to the ascending aorta, filling the anteroposterior diameter of the anterior mediastinum from ascending aorta to sternum. The shadow did not pulsate and was not expansile.

Following the fluoroscopic examination the patient was given 1 mg. of prostigmine and 0.43 mg. of atropine by hypodermic injection. After 15 minutes there was much improvement in articulation and phonation. After 20 minutes there was only slight hoarseness, and the nausea on attempting speech had disappeared. Dyspnea had disappeared. He, himself, was then able to give an account of his illness.

Past history was not significant except for typhoid fever in 1914 and influenza in 1920. He was in excellent health until April 1946 when he noted that he was beginning to tire easily. When he plowed, his head would fall forward on his chest and his "eyes would sink lower and lower" until he was unable to see the ground before him which he was attempting to plow. Exertion beyond this point would result in complete exhaustion. After about 30 days he was unable to plow longer than one hour, and on one occasion, after less than one hour, he was unable to stand or even to sit but had to be taken home in a wagon and lifted into bed. Woodchopping soon became impossible. Recovery was spontaneous and would take place after a few hours' rest. By June 1946 (two months after the onset of symptoms) he had aban-

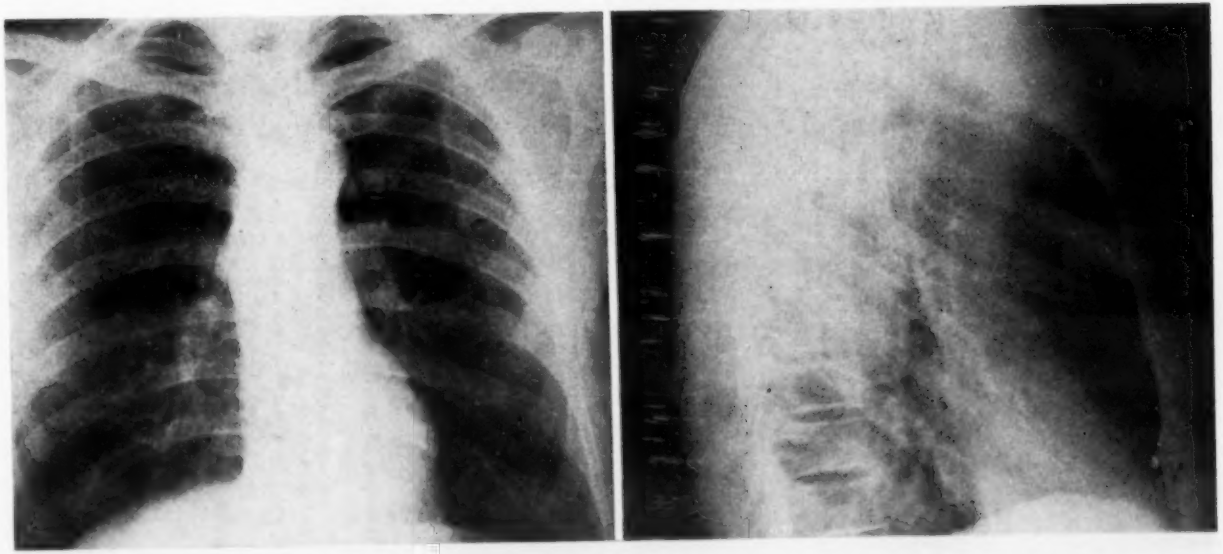

FIG. 1. Posterior-anterior and lateral roentgenograms of chest before operation, showing mediastinal shadow. In the PA view the tumor shadow in the right chest simulates the silhouette of a slightly tortuous aorta.

doned all work but was able to be gainfully employed supervising labor at a sawmill. For one week in June there was some drooping of his right upper eyelid. From the time of onset of symptoms he noted progressive difficulty in chewing and his diet was gradually restricted to soft and liquid foods. Swallowing would become difficult before he could finish a meal. Liquids were occasionally regurgitated through the nose when he attempted to drink. In August (four months after the onset of symptoms) when he presented himself for treatment, he had lost 25 pounds and was subsisting on soda crackers soaked in tomato juice. On two recent occasions he had been seen by physicians who had given him injections of vitamins and had told him that he showed signs of vitamin deficiencies.

Physical examination showed the following positive findings: Temperature 101° F.; pulse 82; respirations 24 (before prostigmine). Blood pressure 110 mm. Hg systolic and 60 mm. diastolic. General appearance of good health, face ruddy but expressionless, moderate dyspnea, hoarse non-productive cough. *Skin:* Moderate thickening and slight scaling over dorsa of hands and feet, scrotal and perineal regions and in suprasternal region. *Eyes:* Slight ptosis of right upper lid, conjunctivae injected. *Mouth:* Mucous membrane reddened with maceration and multiple fissures at angles of mouth. Tongue reddened and atrophic. Teeth extensively carious. Gums reddened, puffy and bleed easily. Palatal reflex sluggish. *Ears:* Slight bilateral loss of auditory acuity. *Chest:* No positive chest findings except coarse grating muscle sounds on expiration. *Genitals:* Left epididymis slightly enlarged. *Extremities:* Small exostosis on head of right fibula. *Neurologic:* Sluggish palatal reflex, ptosis of right eyelid, expressionless facies.

The following laboratory studies were done: blood counts and hemoglobin estimation, urine analysis, blood sugar and non-protein nitrogen, phenolsulfonphthalein excretion test, basal metabolism, and electrocardiogram. There were no abnormal findings. Roentgenograms of the chest confirmed the presence of the mediastinal shadow seen in the fluoroscopic examination (figure 1).

Because of the respiratory symptoms he was given prostigmine bromide tablets, 15 mg. three times daily. Dyspnea did not recur. The voice remained normal. The upper respiratory infection subsided in two days and he became symptom free on bed rest. After two weeks prostigmine was discontinued as he was able to be up and about his house without symptoms. During the prostigmine treatment he was not allowed to exert himself and so was unable to note any effect on exercise tolerance. He did notice that he was able to chew and swallow without tiring while taking the drug.

On September 18, 1946 (five months after onset of symptoms) he was admitted to the Piedmont Hospital, Atlanta, Georgia under the care of Dr. D. Henry Poer for removal of mediastinal tumor. Before operation he was seen in neurologic consultation by Dr. William A. Smith who confirmed the diagnosis of mild myasthenia gravis dependent on exertion.

On September 20, 1946 the tumor was removed by Dr. Poer under nitrous oxide-ether anesthesia. Dr. Poer's operative notes are as follows:

"A curved incision was made along the sternal margin on the right side beginning at the clavicle and extending downward to the seventh rib. The second, third, and fourth ribs were divided near the costo-chondral junctions and about five centimeters of each removed. The tumor was readily found beneath the sternum at this level but in order to permit its removal it was necessary to remove about 60 per cent of the sternum. This permitted adequate exposure for removal of the cystic tumor. This was attached to the pericardium and pleura on the left side and to the large blood vessels posteriorly. The tumor was intimately attached to the vena cava and was dissected free with difficulty. There was no local evidence of spreading of the tumor to surrounding structures and it was felt that it was benign. A definite connection

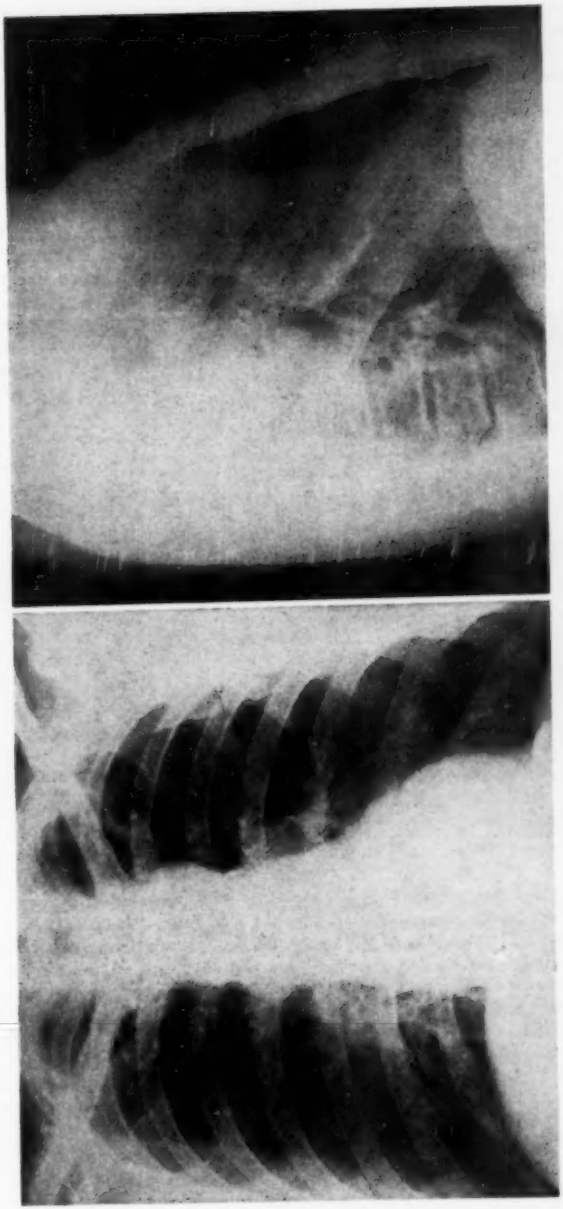

FIG. 2. Posterior-anterior and lateral roentgenograms of chest two months after operation.

with the thymus gland could not be established but its location in the anterior mediastinum suggested this possibility. A small opening in the pleura was closed with small sutures of silk and same was used in closure of the chest wall. The lung was reinflated before closure."

Prostigmine was not needed before or after operation. Penicillin was used three days postoperatively. Patient was able to walk about on fifth postoperative day and left the hospital on the tenth postoperative day.

Pathologic examination of the tumor by Dr. Warren B. Matthews was reported as follows:

"*Gross:* This is an almost spherical structure; its diameter averages four centimeters. The outside is rough and ragged as if removed from surrounding fibrous attachments. The wall is rather tough and thick; it measures up to five millimeters

FIG. 3. Photograph of tumor after removal. The cyst has been opened by longitudinal section. Tissue block for microscopic study has been removed.

in thickness. The lining of the wall is ragged, with a granulation tissue appearance. The cyst contains brownish-yellow, apparently necrotic or clotted matter.

"*Microscopic:* The sections of the cyst wall show that it consists of almost acellular densely collagenous fibrous tissue. This is like old scar tissue with no blood supply. In the wall of the cyst and in the adjacent adherent clot there are many cholesterol crystal clefts. There is a slight granulation tissue reaction in the lining of the cyst. One of the sections reveals some tissue that looks like lymphoid tissue. It consists of tissue which contains lymph follicles that are not very distinct. Careful inspection fails to reveal any evidence of Hassall's corpuscles or other structures identifying this as thymus with certainty. There is no evidence of malignancy.

"*Diagnosis:* Old cyst wall with central degeneration and lymphoid tissue in part of the wall of the cyst. The exact origin of this cyst cannot be stated, although it is undoubtedly congenital."

Three months after operation there was still a recurrent tendency to ptosis of the

right upper lid. Occasionally he would discover that his mouth was hanging open. Some conscious effort was required to keep it closed. He still tired on exertion but chewing was much improved.

Six months after operation (11 months after onset of symptoms) he returned to farming. He prepared and planted 70 acres of land, unaided. He plowed as long as 10 hours a day with nothing more than what he considered a healthy tired feeling at the end of the day. He climbed a 15 foot vertical ladder twice daily to his hay loft, but was still unable to chop wood as this particular exercise produced fatigue of his neck and shoulder muscles rapidly, and caused his head to droop. There was no difficulty in speech, chewing, or swallowing. He gained no weight, probably because of his hard work. Nutrition became excellent, all the signs of early pellagra having disappeared.

On May 23, 1947 after two months of labor (eight months after operation and 13 months after onset of symptoms) he contracted a common cold. Respiratory difficulty

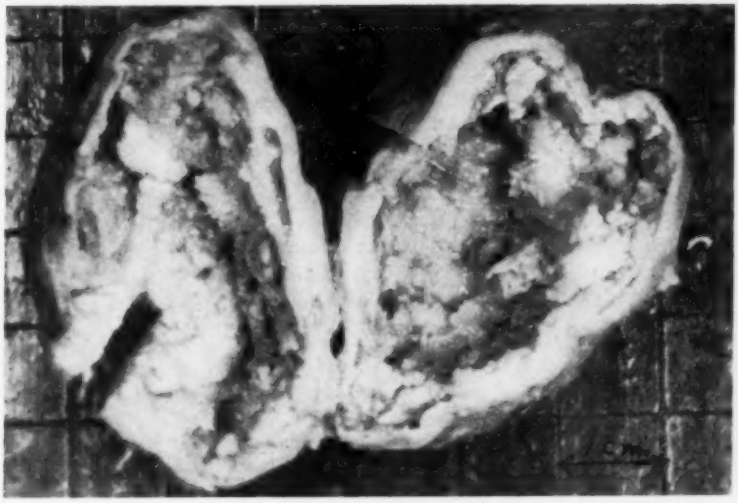

FIG. 4. Interior view of opened cyst.

developed rapidly and swallowing again became difficult. These symptoms were controlled by oral prostigmine. He was able to tolerate 15 mg. by mouth, but 30 mg. caused giddiness, severe abdominal cramping and a short period of syncope. After three days prostigmine was no longer needed. After one week he resumed his usual work.

One year after operation he was in excellent health though still unable to use an axe or hoe. Tough foods still caused the jaw to tire easily, but nutrition was good. No general weakness or drooping of the head had occurred since the acute coryza mentioned above. Chest roentgenograms showed no evidence of recurrence of the tumor.

COMMENT

This man, for 30 years, has been conditioned to arduous labor. He does not consider 10 hours of plowing under semi-tropical weather conditions an unusual

day's work. Although his tumor was probably congenital the symptoms of myasthenia gravis developed abruptly in the fifth decade.

Assuming that this tumor was originally cellular, having had some internal secretory rôle, and later having undergone cystic degeneration, it would be reasonable to expect the onset of symptoms of myasthenia gravis before the occurrence of the cystic degeneration. Assuming that the tumor was from its beginning cystic and essentially acellular, any relationship to myasthenia gravis would seem to have been dependent on its spacial and consequent pressure relationships within the thorax. It is doubtful that these relationships as regards the tumor itself changed after the end of this man's growth period some 30 years before the onset of myasthenia gravis. The history and the pathologic findings make any relationship between the tumor and the myasthenia gravis seem coincidental. .Postoperative remission could have been coincidental also.

Cystic tumors of the thymic region, however, have been repeatedly found at operation and necropsy, and like the primary tumors of the thymus are almost always associated with myasthenia gravis. Histologic proof that these tumors were once cellular seems at present to be lacking. Pathologists describing such tumors are careful to state that the exact origin cannot be determined from the study of the histologic structures. The anatomic relationships of these tumors, including the attachment to the pericardium, suggest a thymic origin. Prior to 1936, when irradiation was the treatment of choice for thymic tumors, it was suggested that cystic changes might have been due to irradiation.[5] Since that time cystic tumors of this region have been encountered in patients who have had no previous radiation therapy.[12] The cystic tumor reported here had not been subjected to radiation.

Blalock's original case had such a cystic tumor.[5] The histologic description by Dr. E. W. Goodpasture is strikingly similar to Dr. Warren Matthews' description of the tumor here reported. In both cases very satisfactory remissions followed surgical removal of the tumor. In Blalock's case the onset of myasthenia symptoms occurred at age 16. In this case occurrence was at age 56.

In discussing the clinical improvement of myasthenia gravis in 20 cases subjected to total thymectomy, Blalock [5] stated that those patients approaching a clinical cure, who were able to discontinue the use of prostigmine after operation, had had symptoms of myasthenia gravis one year or less. The patient here discussed had had symptoms of myasthenia gravis only five months prior to operation. There seems to be among those who have had experience with thymic surgery [5, 17] a feeling that surgical intervention should be limited to those patients with severe myasthenia gravis. It seems probable that with the development of technical skill earlier operation (as soon as myasthenia gravis can be diagnosed) may become a very important part of treatment.

Conclusion

The presence of a benign congenital cystic tumor of the thymic region in a patient who rapidly developed symptoms of myasthenia gravis at age 56 and the successful removal of this tumor followed by prompt and sustained remission of the symptoms of myasthenia gravis are reported.

A few of the relationships between abnormalities of the thymus and myasthenia gravis are reviewed and briefly discussed.

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MASSIVE RESPONSE TO A MERCURIAL DIURETIC IN A CASE OF CONGESTIVE HEART FAILURE*

By PHILIP H. ROSS, M.D., and SIDNEY GRAU, M.D., *Chicago, Illinois*

THE value of mercurial diuretics in the treatment of congestive heart failure is well known. Instances of remarkable response to this medication have been occasionally reported. We recently observed such a case, in which massive diuresis followed the use of mercuhydrin. In our patient the use of this drug produced a greater diuretic response than any heretofore reported in the American literature.

* Received for publication December 20, 1947.
From the Medical Service of Dr. Matthew Taubenhaus, Michael Reese Hospital, Chicago.

Case Report

A 46 year old Negress was admitted to Michael Reese Hospital on August 5, 1947, with symptoms and signs of right heart failure, manifested chiefly by massive anasarca and moderate ascites. Her present illness dated from October 1946, when she first noted swelling of the legs and shortness of breath on exercise. This became progressively more severe and she was hospitalized in another institution in December 1946. According to the patient, her treatment there was "digitalis and shots to make me urinate." She had one subsequent admission to the same hospital with essentially the same complaints, and received similar therapy.

Her first admission to Michael Reese Hospital was on May 3, 1947 with symptoms as above. Detailed history added nothing positive to the present complaints. At that time the significant findings were as follows: The blood pressure was 170 mm. Hg systolic and 130 mm. diastolic. There was slight distention of the neck veins. The fundi were normal. The lungs were clear to percussion and auscultation. The heart was markedly enlarged, the point of maximum impulse being in the sixth interspace in the anterior axillary line. There was a protodiastolic gallop rhythm, with extrasystoles, a systolic murmur best heard at Erb's point, and a loud snapping A_2. The abdomen was distended. Moderate ascites was present, and the skin was markedly edematous. There was four plus edema of the lower extremities, and four plus sacral edema.

The diagnosis at that time was hypertensive heart disease with congestive failure, mainly right, and gallop rhythm. Laboratory tests were essentially negative. Serial electrocardiograms were all definitely abnormal, showing left ventricular preponderance. Roentgen-ray of the chest disclosed a markedly enlarged and globular shaped heart shadow. There was no evidence of pulmonary congestion.

The patient responded well to routine therapy, including the use of digitalis and mercuhydrin. During her 24 day hospital stay she lost 50 pounds, dropping from 178 pounds on admission to 128 pounds on discharge. She left the hospital on May 27, asymptomatic and with only a residual trace of ankle edema.

She was readmitted on August 5, 1947, about 10 weeks later. In this period there had been a progressive return of swelling in the abdomen and legs, and mild dyspnea. Her admission weight was 235 pounds. Apart from the more massive anasarca, physical findings were identical with those on her first admission. Surprisingly, the patient was able to lie flat in bed without increased discomfort. The lung fields were entirely clear to percussion and auscultation. The protodiastolic gallop rhythm was still present. There was massive edema of the abdominal wall, both legs, and the back to the level of the mid-scapula. Moderate ascites was present.

The patient's venous pressure was 25 cm. of water; her arm to tongue circulation time, using calcium gluconate, was 28 seconds. X-ray continued to show a huge, globular shaped heart; however, there was no evidence of pulmonary congestion. In view of the suggestive roentgen findings, a pericardial tap was attempted, but no pericardial effusion was found. Subsequently this finding was confirmed by fluoroscopy, when position changes of the body were unaccompanied by changes in the cardiac silhouette. Electrocardiograms were similar to those of the previous admission.

The patient was continued on routine cardiac management, and slowly redigitalized. The evening of admission, August 5, she was given 2 c.c. of mercuhydrin intravenously. Following this initial dose she voided 13,860 c.c. in a period of 29 hours, and 16,200 c.c. in a period of 41 hours. On August 7 she received her second injection, 2 c.c of mercuhydrin intramuscularly. She voided 4250 c.c. in the 48 hour period following this injection. On August 11 she was given her third injection of mercuhydrin, 2 c.c. intramuscularly, and in the following 24 hours voided 3360 c.c.

By August 12 she was asymptomatic. Ascites, ankle edema and sacral edema were minimal. Her blood pressure, which had been 140/110 on admission, was now

140/100. For the first time since admission the patient left her bed to be weighed. Her weight was now 132 pounds, a loss of 103 pounds in a period of seven days. Her total charted urinary output in this seven day period was 33,300 c.c.

Her blood pressure continued to drop. On August 17 it was 122/80, and remained at approximately this level until discharge. Cardiac fluoroscopy was performed on several occasions. It revealed an enlargement of both the inflow and outflow tracts of the left ventricle, marked enlargement of the right auricle and the inflow tract of the right ventricle. However, the left auricle was not enlarged, and the pulmonary conus area was not prominent. The aorta was widened and dilated. It was felt that these findings were compatible with a Bernheim syndrome,[1] secondary to hypertensive heart disease.

By August 16 the patient's weight had again risen to 136 pounds. She was given 2 c.c. of mercuhydrin intramuscularly, with a resultant nine pound weight loss in 24 hours. She was discharged to the out-patient clinic on August 26, weighing 130 pounds, feeling well, and with only a trace of ankle edema.

Discussion and Summary

Since the popularization of mercurial diuretics in the past two decades, these drugs have taken an important place in the treatment of congestive heart failure. The effectiveness of this group of compounds in the management of cardiac edema has been repeatedly discussed. On the other hand, instances of massive response to single injections of mercurial diuretics have been only infrequently reported. A summary of previous reports on this subject is included in table 1.

Table I

Drug	No. Cases	Maximum Weight Loss	Maximum Urinary Output per Injection	Reference
Salyrgan	60	47 pounds in 4 days	—	Sprague and Graybiel[2]
Mercupurin	22	30 pounds in 1 day	6300 c.c. in 24 hours	Steuer and Wolpaw[3]
Salyrgan	30	14 pounds in 12 hours	11,000 c.c. in 12 hours	Barker and O'Hare[4]
Mercupurin	66	13 pounds in 24 hours	5900 c.c. in 24 hours	Stewart and Wheeler[5]
Mercupurin or Salyrgan	—	—	Average of 2000 c.c. in 24 hours. Up to 8000 c.c. noted	Wheeler[6]
Mercupurin	—	Frequently see loss of 20–40 pounds over a period of weeks	—	Wheeler[7]
Mercuhydrin and Mercupurin	92	12 pounds after one injection. The two drugs similar in effect	—	Modell et al.[8]
Neptal	1	—	14,430 c.c. in 24 hours	Ramsden[9]

Two of these reports merit special mention, in point of degree of responsiveness. In the case reported in England in 1936 by Ramsden,[9] 1 c.c. of Neptal given intramuscularly was followed by a diuresis of 14,430 c.c. in 24 hours. This is an average

output of 600 c.c. per hour. Barker and O'Hare [4] in 1928 reported a diuretic response of 11,000 c.c. in 12 hours, with a concomitant weight loss of 14 pounds, following one injection of salyrgan.

In comparison, our patient voided 13,860 c.c. in 29 hours, or an average output of 480 c.c. per hour. The urinary output after the first injection was 16,200 c.c. in 41 hours. The total urinary excretion after three mercuhydrin injections of 2 c.c. each was 33,300 c.c. in a period of slightly less than seven days. There was a concomitant weight loss of 103 pounds during this seven day period. This represents one of the most massive diuretic responses to a mercurial to be reported to date.

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DANGER OF AIRPLANE FLIGHT TO PERSONS WITH SICKLEMIA *

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THE sickle cell trait (sicklemia) is estimated to occur in 7.4 per cent of Negroes. Only one in 15 cases of sicklemia shows anemia.[1, 6] This disorder of the erythrocytes is inherited as a Mendelian dominant and is confined to persons of the Negro race, with few possible exceptions. In vitro sickling has been shown to depend upon the dissociation of oxyhemoglobin in the red blood cell [4]; when the hemoglobin is in the reduced state the cells sickle, when the hemoglobin is combined with oxygen the cells resume their normal discoid shape. The oxygen tension at which sickling occurs varies from patient to patient, and with different cells from the same patient.[3] Older red cells sickle more readily than young ones. An oxygen tension of 45 mm. Hg has been reported to produce sickling in cells from a patient with active sickle cell anemia [4] while it was necessary to reduce the tension to 18 mm. Hg in the case of cells from a person with sicklemia.[5]

Sicklemia is compatible with normal health and longevity, the persons being free of both symptoms and anemia. Persons with sickle cell anemia seldom live

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beyond 40 years of age, and the majority die before they are 10. Presumably, they have a lower sickling threshold. In sickle cell anemia a chronic normocytic hemolytic anemia develops, and the clinical course is usually characterized by attacks of acute abdominal pain, leg ulcers, neurologic, cardiac, and rheumatoid symptoms.

The precipitating cause of hemolytic crises is unknown, but it is generally accepted that sickling occurs first in the regions of vascular stasis where the oxygen tension is least. Fewer sickled cells are found in arterial than in venous blood.[5] The degree of intravascular sickling can be reduced by the administration of oxygen,[8] although this does not seem to affect the rate of hemolysis. Klinefelter [10] caused a patient with sickle cell anemia to breathe 10 per cent oxygen for 10 minutes. This reduced the oxygen saturation of arterial blood from 89.3 per cent to 51.2 per cent, and at the same time increased the percentage of sickled cells in arterial blood from 19 to 32.

Sickled cells are rigid and fragile. They are two to five times longer than the original diameter prior to sickling. For these reasons it is presumed that sickled cells do not pass readily through terminal capillaries. Stasis of blood results, followed by thrombosis and infarction. As would be expected, the spleen is frequently involved and shows multiple thrombotic lesions. Infarction is common.[7] The cardiac manifestations are due both to the effects of anemia per se, and to the sequelae of sickling: arteritis and endarteritis with thrombosis.[9]

Henderson and Thornell [6] studied 312 Negro aviation cadets and combat veterans, of whom 23 had sicklemia. There was no evidence that this trait interfered with their effectiveness as aviators. Four persons with sicklemia and one with sickle cell anemia were subjected to reduced oxygen tensions. No evidence of increased intravascular sickling was educed in the cases of sicklemia, although it was necessary to administer oxygen to three of them at 10,000 feet. One of these developed extrasystoles which disappeared upon return to normal oxygen tension and pressure. Two developed signs and symptoms of oxygen deficiency not unusual for healthy subjects under the same conditions. The fourth case withstood 16,000 feet for five minutes without the administration of additional oxygen. The person with sickle cell anemia withstood the lowered oxygen tension better than normal controls or the sicklemia subjects. He did, however, give suggestive evidence of increased intravascular sickling.

Findlay, Boulter, and MacGibbon [11] took three African volunteers with sickle cell trait up to 15,000 feet above sea-level without additional oxygen. All had total red cell counts between 4 and 5 million per cu. mm. Venous blood was drawn under oil and immediately fixed in 10 per cent formol saline. Samples taken at sea level, 5000 feet and 10,000 feet failed to reveal sickling, but after 15 minutes at 15,000 feet a slight degree of sickling was noted in all subjects (0.8, 1.2, and 5.0 per cent sickled cells). Following flight there was no increase in reticulocytes, icterus index, or urine urobilinogen. Findlay states, "Though flying for a short time at 15,000 feet does not necessarily induce a sickling crisis through reduction of oxygen tension, it may obviously cause an increased rate of sickling and, as Africans vary in the reduction of oxygen tension necessary to produce sickling, it is possible that sooner or later an African will be found who will sickle when flown at 10,000 or 15,000 feet for a comparatively short time." He recommends that oxygen be carried on all planes in which Africans are passengers.

The following case is presented to illustrate the effect on a case of sicklemia

of a more prolonged exposure to reduced oxygen tension. It will be noted that there was no anemia, and that his symptoms occurred when high altitude was reached on two occasions. Though no studies were made to correlate the lowered oxygen tension he experienced in flying over the Rocky Mountains in a commercial airliner with the reduced oxygen tension required to produce sickling of his erythrocytes in vitro, it seems fair to assume that the diminution of oxygen tension he experienced in flight precipitated intravascular sickling with resultant splenic infarction and multiple small thrombi in the myocardium.

Case Report

An 18 year old colored male was completely well until he travelled from the East Coast to California by air, May 1, 1947. He became "air sick" and vomited considerably. Associated with this was a dull heavy ache in the left upper quadrant of the abdomen. When he left the plane nausea and vomiting were relieved, but the abdominal distress persisted for six days. On May 12, upon the expiration of his furlough, he began the return journey. As soon as the plane attained maximum altitude for flight over the Rocky Mountains, estimated to be between 10,000 and 16,000 feet above sea level, he experienced nausea and a cramping pain in the left upper quadrant. There was no vomiting. Again the abdominal pain persisted several days. It was aggravated by walking and jarring of the body. He was admitted to the Station Hospital, Ft. Belvoir, May 15, 1947, and transferred to Walter Reed General Hospital, June 11, 1947.

Family and previous personal history were non-contributory. There had been no evidence of anemia. He had had frequent pretibial wounds since the age of eight, but these always healed promptly, and he felt that they were always accounted for by trauma.

Physical examination revealed a well developed, well nourished, colored male, 69 inches tall, weighing 169 pounds. His blood pressure was 120 mm. Hg systolic and 88 mm. diastolic, temperature 99° F. The skin showed numerous linear striae over both shoulders and in the lumbar region. Skin over anterior surface of tibiae showed moderate scarring. Lungs were clear. Heart was not enlarged, rate 72, marked sinus arrhythmia, sounds were of good quality. The second sound was reduplicated at the apex. No murmurs were heard. Abdominal examination revealed moderate tenderness in the left upper quadrant, and a firm mass 15 cm. in diameter was felt in this region. Liver and kidneys were not felt.

Because of the enlarged spleen and his race, sickle cell anemia was considered a likely diagnosis. Sickling was demonstrated by the usual moist smear technic. Anisocytosis, marked poikilocytosis, hypochromia, and slight target cell formation were noted. Increased resistance of the erythrocytes to hemolysis in hypotonic saline was demonstrated by a fragility test: Patient, initial hemolysis 0.36 per cent, hemolysis not complete at 0.28 per cent; control, initial hemolysis 0.42 per cent, complete hemolysis 0.36 per cent. Blood counts are shown below:

	RBC	Hb.	WBC	N	L	Sickling
May 15	—	—	19,450	80	20	
May 17	4.8	14.5	16,000	73	23	+
May 20	4.5	13.5	5,050	58	33	+
May 29	—	—	7,400			
June 12	4.7	14.7	8,150	59	40	
June 27	5.1	14.1	7,250	56	39	+
July 9	5.7	16.0	7,300	63	27	

Blood Kahn was negative, no cold agglutinins were present; urine urobilinogen was not present in dilutions of more than 1:10. Roentgenograms of the chest and skull were normal, flat plate of abdomen revealed the enlarged spleen. Electrocardiograms showed low voltage of T_3, inverted T_3, notching of T_4 with inversion of T_4 later, and still later, T_4 returned to upright position and T_3 became normal. PR intervals were normal on all tracings (figure 1).

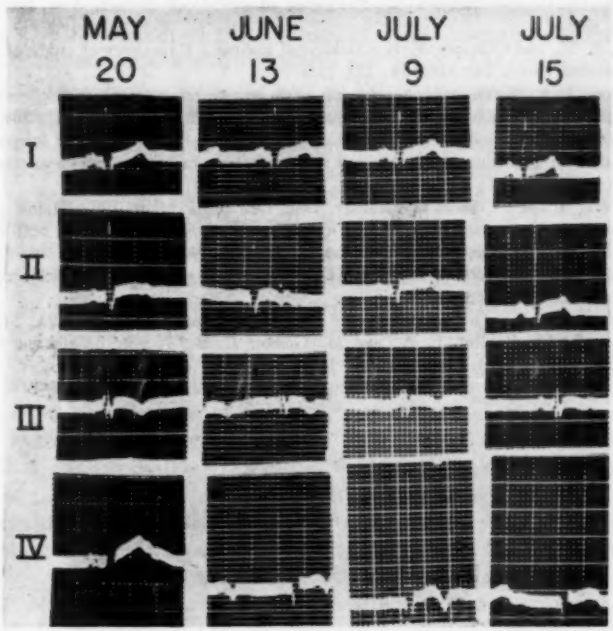

FIG. 1. EKG in case of sicklemia following airplane flight. See text for explanation.

The patient became asymptomatic shortly after admission, but there was little recession in the size of the spleen in the two months of observation. He was discharged from the service for physical disability.

It is felt that this case indicates an aspect of military medicine deserving of further investigation. If it is shown that intravascular sickling is regularly precipitated in persons with sicklemia by airplane flight, this fact will have to be considered before Negroes are employed as airborne troops or aircraft crews.

SUMMARY

1. A case is presented of sicklemia with sudden splenic enlargement and electrocardiographic abnormalities following airplane crossing of the Rocky Mountains.

2. Attention is called to the dangers of anoxemia in persons with sicklemia or sickle cell anemia.

3. The high incidence of sickle cell trait in Negroes is mentioned, and some military implications suggested.

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EDITORIAL

ENCEPHALITIS FOLLOWING VACCINATION AGAINST PERTUSSIS

SEVERE injury of the brain ("encephalitis") and spinal cord has been observed as an immediate or early sequel of many immunization procedures, including the inoculation of living vaccines, killed bacterial suspensions or other culture materials, and prophylactic antisera. The incidence of such reactions is, in general, extremely low, so low that any one individual even if actively engaged in this type of work is likely to see only a few such cases in a life time. The results of such injuries, however, are often so devastating that the possibility of their occurrence should be generally realized.

The earliest recognized and best known instance of such an encephalitis is that following the Pasteur immunization against rabies. In spite of the fact that such cases have been observed and studied for more than 50 years, there is still no agreement as to their pathogenesis. The encephalitis is not, however, an attenuated attack of rabies caused by virus introduced by the bite but is a direct result of the immunization. Its incidence is probably about one in 1000 cases.

Encephalitis may also occur as a sequel of vaccinia. Although vaccination has been practiced for 150 years, serious neurological sequelae apparently were not recognized until about 25 years ago. The first adequate report, that of Turnbull and McIntosh (1926),[1] described seven cases. Shortly after this a considerable number of cases were observed both in Great Britain and on the European continent, and its widespread although infrequent occurrence is now well recognized. The incidence is usually very low, about one in 10,000 to one in 30,000 cases of vaccination. It occurs chiefly in older children and young adults after the first vaccination, practically never in infants. Partly for this reason it is relatively rare in the United States.

The symptoms are characteristic and appear 10 to 12 days after vaccination, at the height of the cutaneous eruption. The onset is abrupt with fever, malaise, headache, pain in the back, vomiting and drowsiness. This progresses rapidly to coma, often in association with convulsions, accompanied by flaccid paralyses of the legs, loss of reflexes, frequently bulbar palsy, and other evidences of focal brain injury. Death occurs in about 50 per cent of the cases, usually after five or six days, but those who survive usually recover completely or nearly so. The pathogenesis of this disturbance is also still uncertain.

Recent observations indicate that grave injury to the nervous system with symptoms resembling those described in postvaccinal encephalitis may follow the administration of pertussis vaccine. Several observers over the past 15

[1] Turnbull, H. M., and McIntosh, J.: Encephalomyelitis following vaccination, Brit. J. Exper. Path. 7: 181–222, 1926.

years, in reports concerned primarily with the effectiveness of the vaccination, have mentioned or described isolated instances of such reactions (Madsen,[2] Doul et al.,[3] Taylor,[4] Kendrick et al.,[5] Sako et al.,[6] Werne et al.,[7] Brody [8]). The first systematic study was that of Byers and Moll,[9] who reported 15 cases observed at the Children's Hospital in Boston over a period of 10 years. The manifestations were quite similar in most of the cases, and they constitute a clear cut clinical syndrome.

The age of the children affected ranged from six to 18 months at the time of the vaccination, and 12 of the 15 were males. The children were regarded as normal before the vaccination, and in none had convulsions been observed. The usual dose of fluid vaccine was given in 12 cases, and in the others it was combined with diphtheria or tetanus toxoid or both.

Symptoms appeared after an interval of from 20 minutes to 72 hours following the injection, in 12 cases within 12 hours. The onset was usually abrupt with high fever, restlessness, irritability or drowsiness, followed quickly by generalized or occasionally unilateral convulsions and coma. Usually there were evidences of gross organic cerebral lesions. These included hemiplegia or hemiparesis in several, and generalized spasticity with exaggerated reflexes and positive Babinski sign. In one case reported by Brody, the third severe reaction to successive injections of vaccine was followed by a persisting generalized flaccid paralysis including bulbar palsy and weakness of the sphincters, and death from pneumonia occurred seven weeks later.

All 15 cases of Byers and Moll survived the acute illness which subsided after two to 10 days. Two subsequently died of pneumonia in other institutions after periods of progressive deterioration of six and 18 months, respectively. At autopsy in one of these, "diffuse atrophy and gliosis of the brain" were found.

Subsequent examination of these cases showed reasonably satisfactory recovery in only one. In three instances, the interval was too short to warrant final conclusions, but in the nine others there were serious and almost certainly permanent sequelae of varying severity. Of the 13 surviving children, recurrent convulsions persisted in nine. Cerebral palsies were present in seven, two of whom were blind. Two were "virtually decerebrate."

[2] Madsen, T.: Vaccination against whooping cough, J. A. M. A. **101**: 187–188, 1933.
[3] Doul, J. A., et al.: Active immunization against whooping cough, Am. J. Pub. Health **26**: 1097–1105, 1936.
[4] Taylor, H. W.: Reaction following injection of pertussis vaccine-Sauer, Arch. Pediat. **55**: 572, 1938.
[5] Kendrick, P., and Eldring, G.: A study in active immunization against pertussis, Am. J. Hyg. **29**: 133–153, 1939.
[6] Sako, W., et al.: Early immunization against pertussis with alum precipitated vaccine, J. A. M. A. **127**: 379–384, 1945.
[7] Werne, J., and Garrow, I.: Fatal anaphylactic shock. Occurrence in identical twins following second injection of diphtheria toxoid and pertussis antigen, J. A M. A. **131**: 730–733, 1946.
[8] Brody, M.: Neurological complications following administration of pertussis vaccine, J. A. M. A. **140**: 555–556, 1949.
[9] Byers, R. K., and Moll, F. C.: Encephalopathies following prophylactic pertussis vaccine, Pediatrics, **1**: 407–457, 1948.

Four of these had walked before their illness. Six showed mental retardation, and one of these, in addition to the two fatal cases, was grossly defective. The electroencephalograms (in 12 cases) showed gross abnormalities in four, slowed rhythm in four and were regarded as normal in four. Pneumoencephalograms in 10 cases showed border-line normal records in two and abnormalities in eight, including dilatation of one or both lateral ventricles. In several these were marked and indicated severe cortical atrophy.

In an effort to determine the frequency of such reactions, Toomey [10] circulated a questionnaire asking specifically regarding the occurrence of convulsions after pertussis vaccination. He obtained reports of "at least 38 authentic cases" from 17 different sources. There were two deaths. All of 12 cases reported to him by Buchanan are said to have shown "irreversible changes." Twenty-three were said to have recovered completely. Although investigations of this type are unsatisfactory in many respects, this does in general confirm the observations of Byers and Moll. The greater severity of the cases reported by the latter is probably due to the fact that all of their patients were brought to the hospital because of the severity of the reactions. Milder cases which presumably may have occurred would not have been observed. Although no precise figures can be given regarding the frequency of such reactions, they are obviously rare, since the 38 cases represent the combined experience of many observers who collectively had administered pertussis vaccine to many thousands of other children without untoward results.

Byers and Moll reported that in the 10 year period during which their 15 cases had occurred, eight cases of postvaccinal encephalitis had been admitted to the Children's Hospital and 28 cases of "encephalitis" complicating an attack of pertussis had been observed. Since vaccination against smallpox presumably was carried out in a larger proportion of the population than the administration of pertussis vaccine, the incidence of encephalitis following the latter in that area seems to have been more than double that of postvaccinal encephalitis and fully equal to that of the encephalitis occurring spontaneously during an attack of pertussis.

Additional confirmation is furnished by Globus and Kohn [11] who have since reported two similar cases. One patient died on the thirtieth day, after showing clinical signs of increased intracranial pressure. At autopsy the brain was very soft, so that it was difficult to make out the surface markings. "The cerebral cortex was entirely devoid of its normal architecture." "Practically no nerve cell had retained its normal structure." There were large numbers of macrophages containing fat granules, both in the cortex and subcortex. There was a "total absence of vascular changes," no perivascular lymphocytic infiltrations, no necroses in the vessel walls and no hemorrhages. They regarded the changes as purely degenerative.

[10] Toomey, J. A.: Reactions to pertussis vaccine, J. A. M. A. **139**: 448–449, 1949.
[11] Globus, J. H., and Kohn, J. L.: Encephalopathy following pertussis prophylaxis, J. A. M. A. **141**: 507–509, 1949.

The pathogenesis of this encephalitis has been the subject of much speculation, but it is still not established. It is not due to contaminated or faulty vaccine. Some have suggested that it is due to the action of specific bacterial toxins contained in the vaccine. The formation of toxins by *Hemophilus pertussis* has been demonstrated, but these are extremely unstable substances, and it seems unlikely that they could retain their activity in the vaccine for any significant period of time. Autopsy material is too scanty to warrant any conclusions, although the little available suggests a toxic or degenerative process rather than a local infection.

There are many analogies between this condition and the encephalitis following vaccinia, rabies vaccine, and that occurring rarely during such infections as variola, varicella, rubella and rubeola. The pathogenesis of the neurological lesions in these diseases, however, is also uncertain. One might expect that in these infections there was an unusual localization of the virus in the brain. The tissues have been studied in a considerable number of cases, but there is a sharp difference of opinion among pathologists as to whether the lesions are primarily inflammatory or degenerative. Most of the cases have shown some degree of perivascular infiltration of lymphocytes, usually slight or moderate, as well as degenerative changes in the nerve cells of varying severity and extent. The most characteristic feature, which is common to all of these conditions, is the occurrence of perivascular areas of demyelinization, especially about the smaller veins, with little or no infiltration with lymphocytes. Many phagocytes stuffed with fat droplets are usually present, but these are largely of the gitter cell type and are believed to be derived from neuroglia. These lesions resemble those found in multiple sclerosis and acute disseminated encephalomyelitis, which are regarded by many investigators as primarily degenerative processes. The lesions differ from those in such infections as poliomyelitis and epidemic encephalitis, in which the nervous tissue is directly invaded by the virus and in which there is marked perivascular infiltration with lymphocytes but no such foci of demyelinization. These points have been discussed extensively by Ferraro.[12]

The close similarity of the encephalitic lesions in all of these conditions, vaccinia, antirabies vaccination, variola, varicella, measles, suggests although it does not prove that the same mechanism is involved in the production of all of them. This has led to the suggestion that they are caused by some unrelated virus which had been present in the individual in a latent state and was activated by the vaccination or the infection. This view is purely speculative, however, since no one has been able to demonstrate such a virus, and it is not generally accepted.

The rarity of such attacks strongly suggests that, whatever the mechanism, they must depend in part upon some individual peculiarity or predisposition. The view that they are the result of a local allergic reaction

[12] Ferraro, A.: Pathology of demyelinating diseases as an allergic reaction of the brain, Arch. Neurol. and Psychiat. **52**: 443–483, 1944.

(antigen-antibody reaction) has been supported among others by Ferraro [12] (especially from the histological standpoint) and by Finley.[13] The latter has emphasized that the appearance of encephalitis in variola, measles and vaccinia is usually on the tenth to fourteenth day, when the local reaction is at its height and the development of hypersensitiveness is to be anticipated.

In these cases as well as those showing encephalitis after pertussis vaccine, manifestations of a generalized anaphylactic reaction are unusual, and one must assume a localized reaction in which the brain functions as the shock organ. There is experimental evidence to support such a possibility. Rivers and Schwentker,[14] Ferraro [12] and others have produced extensive demyelinating lesions in the brains of monkeys, closely resembling those in multiple sclerosis, by administering a long series of injections of suspensions of rabbit brain tissue. It has been shown that such animals develop precipitins and complement-fixing antibodies in their serum which are specific for brain tissue from any source but not for the body proteins of the species of animal from which the brain tissue was derived. More recently Morgan [15] and Kabat et al.,[16] using an improved technic, have produced very extensive lesions of a similar character by a few injections of homologous brain tissue.

In the cases of encephalitis following pertussis vaccine, the symptoms have usually appeared within a few hours, and previous sensitization must be assumed. Opportunity for this is obvious in cases in which the encephalitis followed the second or third injection, but in six of the cases of Byers and Moll and in several collected by Toomey, it followed the initial dose. Although a previous unrecognized attack of pertussis can not be absolutely excluded, it is unlikely that this had occurred in all of these cases. In the cases of horse serum, however, many of the fatal reactions have followed the first injection of antitoxin, and it must be recognized that occasional individuals can become highly sensitive to substances with which they apparently have had no previous contact.

There is evidence in some of these cases that hypersensitiveness is increased by the injection of vaccine. In two of Byers and Moll's cases, a fairly severe reaction (but without neurological manifestations) had followed the preceding injection of vaccine. In three of their cases and in two of Brody's, in spite of severe reactions with evidence of brain injury, subsequent injections of vaccine were nevertheless given, and all were followed by reactions of even greater violence. In two cases negative local reactions were reported following subsequent intradermal injections of pertussis vaccine to test for hypersensitiveness. In the case of Brody mentioned

[13] Finley, K. H.: Pathogenesis of encephalitis occurring with vaccination, variola and measles, Arch. Neurol. and Psychiat. **39**: 1047–1054, 1939.

[14] Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys, J. Exper. Med. **61**: 689–702, 1935.

[15] Morgan, I. M.: Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue, J. Exper. Med. **85**: 131–140, 1947.

[16] Kabat, E. A., et al.: Rapid production of acute disseminated encephalomyelitis in rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants, J. Exper. Med. **85**: 117–130, 1947.

above, this was followed immediately by a severe exacerbation of the neurological disturbances.

Similar reactions with manifestations of encephalomyelitis have been observed in rare instances after injections of foreign protein of other types; e.g., horse serum (Kennedy,[17] Winkleman and Gotten [18]), coli-streptococcus vaccine,[18] and typhoid vaccine.[17]

Although the evidence is not conclusive, it seems probable that the encephalitis following pertussis vaccine is due to a local allergic (antigen-antibody) reaction. The same may well be true of the cases associated with smallpox and rabies vaccine and the viral infections. The similarity of the pathologic lesions in the brain, however, is not adequate proof that the same etiologic factor is concerned in all of them.

One may conclude that the administration of pertussis vaccine involves a definite but remote risk of causing a damaging encephalitis. It is comparable in its incidence to that of the encephalitis following smallpox vaccination; its immediate mortality has been less, but the frequency of severe permanent injury to the brain has been higher. The mortality of pertussis in young children is so high, however, and the protective value of the vaccine so well established that the remote risk of encephalitis should not interfere with the widespread use of the vaccine.

Certain precautionary measures, however, are definitely indicated. All cases should be observed following administration of the vaccine and further doses withheld if severe reactions occur and particularly if there are convulsions or any other reasons to suspect cerebral injury. As a rule it should not be given to children with fever or other evidence of acute illness. It seems prudent to use special caution in cases with evidence of cerebral damage of other types and in those who have shown manifestations of hypersensitive reactions, although there is as yet no direct evidence that encephalitis has occurred more frequently in either group. It is also important that all such reactions be observed and recorded, so as to furnish more precise information as to their incidence, their nature, and the existence of possible predisposing factors.

P. W. C.

[17] Kennedy, F.: Certain nervous complications following use of therapeutic and prophylactic sera, Am. J. M. Sc. **177**: 555, 1929.

[18] Winkleman, N. W., and Gotten, N.: Encephalomyelitis following the use of serums and vaccines, Am. J. Syph. and Neurol. **19**: 414–424, 1935.

REVIEWS

The Thyroid and Its Diseases. 2nd Ed. By J. H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University and Chief of the Medical Services, Massachusetts General Hospital. 571 pages; 15.5 × 23.5 cm. J. B. Lippincott Company, Philadelphia. 1948. Price, $12.00.

In his introduction to the first edition of this work, published in 1937, Dr. Means described it as "an account of the personal experiences of a considerable group of workers in a single thyroid clinic, and of the opinions and convictions derived from this experience." The second edition carries further the studies of the same group under Dr. Means working in the Thyroid Clinic of the Massachusetts General Hospital, and in association with investigators of several other institutions. Three chapters are contributed by associate authors. The section on pathology of the thyroid, and that devoted to discussion of tumors, are written by R. W. Rawson, Assistant Professor of Medicine, Harvard University. The chapter on surgery of the thyroid gland is the work of Oliver Cope, Assistant Professor of Surgery, Harvard University.

Remarkable changes have occurred in the management of hyperthyroidism during the past few years. The anti-thyroid drugs have played the greatest part in the newer therapeutic approach, but the use of radio-active iodine is an ever increasing factor in the diagnosis and treatment of thyroid hyperplasia, and has even led to the reëstablishment of the old clinical concept of Plummer's toxic adenoma, which is now accepted as a true entity, after a dispute that lasted for many years. Unfortunately, the description of the action and uses of radio-active iodine is not treated quite as fully as might be hoped, because of rapid progress made in this field since the publication of the book. The relatively recent availability of the 8-day isotope from Oak Ridge has lessened the significance of the treatment data presented, which are based on the 12-hour cyclotron product.

Very complete descriptions are given of the anatomy, physiology and pathologic physiology of the thyroid. The descriptions of myxedema and cretinism are masterpieces and only slightly less interesting than the discussion of Graves' disease and its complications.

"The Thyroid and Its Diseases" is easy to read, informative and authoritative.

T. N. C.

Atlas of Peripheral Nerve Injuries. By WILLIAM R. LYONS, Ph.D., Associate Professor of Anatomy, University of California Medical School, and BARNES WOODHALL, M.D., Professor of Neurosurgery, Duke Medical School, Durham, N. C. 339 pages; 25 × 33 cm. W. B. Saunders Company, Philadelphia. 1949. Price, $16.00.

The authors have assembled an imposing volume of data on peripheral nerve injuries. This book well summarizes our present knowledge of the histopathology of peripheral nerve trauma and regeneration. The factual material it contains will assist the neurosurgeon in determining the proper management of a peripheral nerve lesion. The neuropathologist will find the book of value in evaluation of peripheral nerve pathology. All investigators whose problems are related to the peripheral nerves will find this Atlas a valuable reference.

The first chapter is devoted to the methods employed in the study of the vast material acquired from peripheral nerve injuries during the recent war. The second chapter details the terminology used and presents by text and illustrations the normal anatomy of the peripheral nerve. Chapters three and four discuss severed

nerves and nerve lesions in continuity. The gross and microscopic anatomy of the pathologic nerve is carefully discussed and beautifully illustrated. The proximal and distal neuromatous formations are extensively considered in terms of their various histologic components. Chapter five deals with all aspects of nerve sutures and suture materials, with emphasis upon reasons for surgical failures. The final chapter deals with the problem of various types of nerve grafting.

The book, undoubtedly, fills the need for a source book for the histopathology of peripheral nerve injury, and should have a warm welcome from neuropathologists and neurological surgeons.

R. K. T.

Headache and Other Head Pain. By HAROLD G. WOLFF, M.D. 642 pages; 16 × 24.5 cm. Oxford University Press, New York 11, N. Y. 1948. Price, $12.00.

This book is a real contribution to clinical medicine in dealing with a subject perplexing to all practitioners. The volume accomplishes the dual physio-pathologic approach in most illuminating fashion. Experimental evidence is presented interestingly and completely. Bibliography and graphic charts amplify the text. Its shortcoming lies in the inadequate elaboration of the psychogenic factors of headache. Nevertheless, it is a contribution to the literary and clinical armamentarium of the student, clinician, and research worker.

H. W. N.

Diabetic Menus, Meals and Recipes. By BETTY M. WEST. 254 pages; 14.5 × 22 cm. Doubleday & Company, Inc., New York 20, N. Y. 1949. Price, $2.95.

The author of this book on dietetics for the diabetic patient is herself a diabetic. In her introduction she states that her purpose is to simplify the problem for the individual who has just discovered that he has the disease. The reviewer believes that this aim of simplification has not been reached, and that the book suggests a far too complicated method of life for the patient, unless he is willing to make diabetes his life's work.

A few useful recipes are included and this particularly applies to directions for making soups, when enough may be prepared for the entire family and divided proportionately. However, many of the items are single servings and, in the opinion of the reviewer, who is also diabetic, this method of cooking single servings isolates the patient too much from the rest of the family.

The book is not recommended fully, though it may be useful for the professional dietitian.

T. N. C.

A Textbook of Pharmacognosy. 5th Ed. By GEORGE EDWARD TREASE, B.Pharm., Ph.C., F.R.I.C., F.L.S., Reader in Pharmacognosy and Head of the Department of Pharmacy in the University of Nottingham. Revised with the assistance of H. O. Meek, Ph.C., H. E. Street, B.Sc. Ph.D., Ph.C., and E. O'F. Walsh, B.Sc., Ph.D., A.R.I.C., Ph.C. 811 pages; 14.5 × 22.5 cm. The Williams and Wilkins Co., Baltimore. 1949. Price, $8.00.

This textbook was originally published for the purpose of preparing students for pharmaceutical examinations. This latest (fifth) edition nevertheless covers the field of pharmacognosy satisfactorily, and in addition contains discussion of such topics as: London commerce in crude drugs, enzymes found in vegetable drugs, chemistry of drug constituents, drug extraction, fluorescence and chromatographic analysis, and exercises on the evaluation of crude drugs. In addition, 10 maps are given (at the end of the text) showing the distribution of crude drugs throughout the world.

The text has been "revised in accordance with the U.S.P. XIII, 1947, and the B. P. 1948." As a result, the drugs which are official in the present Pharmacopoeia are so indicated; while the present National Formulary crude drugs, although included, are not designated as such. It is noted that the doses of all drugs have been omitted although this is in direct contrast with the average American pharmacognosy text.

The illustrations and the photographs are clear-cut and the type is easily readable. The uses of the crude drugs are given in a simple, easy-to-understand manner. The preparation and commercial aspects of some crude drugs, e.g. cinnamon, opium, tragacanth, are discussed in great detail and are well illustrated.

This text ranks with the leading American pharmacognosy textbooks and should be included as one of the recommended texts. From the standpoint of the internist the book should prove to be of interest as a reference text.

F. J. S.

Psychotherapy: Its Uses and Limitations. By D. Rhodes Allison and R. G. Gordon. 160 pages; 12.5 × 19 cm. Oxford University Press, New York 11, N. Y. 1948. Price, $3.00.

This book attempts to cover the various aspects of psychotherapy with respect to its use in the organic diseases, the psychoses, the neuroses, psychosomatic states, the mental deficient, and psychopathic personality. It is a weak-hearted appeal for the considered use of psychotherapy with little that is illuminating. The paucity of clinical material makes it inadequate for use by the clinician or medical student.

H. W. N.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Biological Antioxidants: Transactions of the Third Conference, October 7–8, 1948, New York, N. Y. Edited by Cosmo G. MacKenzie, Department of Biochemistry, Cornell University Medical College; Associate Editors: Richard H. Barnes, Sharp and Dohme, Inc., Leslie Hellerman, The Johns Hopkins School of Medicine, and Karl E. Mason, School of Medicine and Dentistry, University of Rochester. 146 pages; 23.5 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr., Foundation, New York. Price, $2.70.

Blood Clotting and Allied Problems: Transactions of The Second Conference, January 24–25, 1949, New York, N. Y. Edited by Joseph E. Flynn, Department of Pathology, Columbia University. 231 pages; 23 × 15 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, $2.25.

Chemotherapy of Leukemia and Leukosarcoma: A reprint of an exhibit presented at the American Medical Association Convention, Atlantic City, June, 1949. By William Dameshek, M.D., Marvin L. Bloom, M.D., Louis Weisfuse, M.D., Milton H. Freedman, M.D., and Miguel Layrisse, M.D., New England Center Hospital—Tufts College Medical School, Boston, Massachusetts. 54 pages (printed on one side only); 32 × 23.5 cm. (loose-leaf, paper-bound). 1950. Grune & Stratton, Inc., New York. Price, $4.75.

The Heart and the School Child: A Symposium. Edited by Jacob M. Cahan, M.D., F.A.C.P. Contributors: Rachel Ash, M.D., William Dunbar, M.D., Mary H. Easby, M.D., F.A.C.P., George Howard Gehrmann, M.D., F.A.C.P., Ed-

WARD E. HOLLOWAY, M.D., MARSHALL M. LIEBER, M.D., D. STEWART POLK, M.D., and MARTIN H. WENDKOS, M.D., F.A.C.P. 94 pages; 21 × 13 cm. 1949. Neo-Aesculapian Press, New York. Price, $2.50.

Metabolic Interrelations: Transactions of the First Conference, New York, N. Y., February 7–8, 1949. Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York, N. Y. 193 pages; 23 × 15 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, $2.95.

Physiology of Heat Regulation and the Science of Clothing: Prepared at the Request of the Division of Medical Sciences, National Research Council. Edited by L. H. NEWBURGH, M.D., Professor of Clinical Investigation, The Medical School, University of Michigan. 457 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $7.50.

Physiology of the Nervous System. 3d Ed. By JOHN FARQUHAR FULTON, O.B.E., M.D., D.Sc., LL.D., Sterling Professor of Physiology, Yale University, etc. 667 pages; 22.5 × 15 cm. 1949. Oxford University Press, New York. Price, $10.00.

The Physiology of Thought: A Functional Study of the Human Mind in Action. By HAROLD BAILEY, M.D., F.A.C.S. 314 pages; 23.5 × 15.5 cm. 1949. The William-Frederick Press, New York. Price, $3.75.

Principles and Practice of Therapeutic Exercises. By HANS KRAUS, M.D., Assistant Clinical Professor of Rehabilitation and Physical Medicine, New York University College of Medicine, etc. 309 pages; 23.5 × 16 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price $6.50.

St. Thomas's Reports—Second Series, Vol. V. Editors: DR. H. K. GOADBY, DR. J. S. RICHARDSON, assisted by DR. J. H. CYRIAX, DR. H. J. WALLACE. 136 pages; 25.5 × 15.5 cm. 1949. St. Thomas's Hospital, London. Price, 10s. 6d.

Secretory Mechanism of the Digestive Glands. 2nd Ed. By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C., Formerly Research Professor of Physiology, McGill University, Montreal, Canada, etc. 1027 pages; 24.5 × 16 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $20.00.

Therapie der Übertragbaren Kinderlähmung, Die—. By PROF. DR. KURT HOFMEIER. 112 pages; 21 × 15 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, Kart. DM 7.50.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1950–51

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1950–51, are herewith announced:

President-Elect ..... Maurice C. Pincoffs, Baltimore, Md.
First Vice President ..... Ernest H. Falconer, San Francisco, Calif.
Second Vice President ..... Edgar Hull, New Orleans, La.
Third Vice President ..... Arthur T. Henderson, Montreal, Que.

Regular elections will take place at the 1950 Annual Session in Boston, Mass., April 20, 1950, the date of the Annual Business Meeting at Mechanics' Building, general headquarters.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
Marion A. Blankenhorn, Cincinnati, Ohio
LeRoy H. Briggs, San Francisco, Calif.
David W. Carter, Jr., Dallas, Tex.
J. Edwin Wood, Jr., Charlottesville, Va.
Harold H. Jones, Chairman, Winfield, Kans.
Committee on Nominations

Notice to Fellows and Masters Concerning Amendments to the By-Laws, A.C.P.

The Board of Regents on November 13, 1949, unanimously approved the following amendments to the By-Laws, and instructed the Secretary to present them for final ratification at the next Annual Business Meeting of the American College of Physicians during the Thirty-first Annual Session at Boston, April 20, 1950. These amendments have as their purpose the recognition of the recently created Medical Service of the U. S. Air Force, on the same basis as the Medical Corps of the U. S. Army, U. S. Navy, U. S. Public Health Service and the Veterans Administration, by which the Medical Service of the Air Force shall have representation on the Board of Governors of the College.

By-Laws, Article IV, Board of Governors, section (1), line 7 to read, "Board of Regents; one each from the United States Army, Navy, *Air Force*, Public . . ."

By-Laws, Article V, Election of Fellows, section (2), line 6 to be revised to read, "he resides, or by the Surgeon General of the Army, Navy, *Air Force*, or Public Health. . . ."

By-Laws, Article VII, Election of Associates, section (2), line 7 to read, "Navy, *Air Force* or Public Health Service or the Medical Director of the Veterans . . ."

The only amendment, therefore, is the insertion of the words "Air Force" at the three points indicated.

A.C.P. Endorses William Crawford Gorgas for New York University Hall of Fame

The Executive Committee of the Board of Regents of the American College of Physicians has unanimously adopted the following resolutions:

"Resolved by the American College of Physicians, that this Association endorses and approves of the effort of the Gorgas Hall of Fame Committee to endeavor to have the name of Dr. William Crawford Gorgas inscribed in the New York University Hall of Fame; and

Resolved Further, that the officers of this Association are authorized to join with others in furtherance of this worthy purpose, and to present the name of Dr. Gorgas in behalf of this Association at the appropriate time."

A.C.P. Restricts Its Activities to Scientific and Educational Affairs

On December 9, 1949, many newspapers of America carried announcements concerning utterances of Oscar R. Ewing, U. S. Federal Security Administrator, during an interview in London concerning nationalized medicine and the British health plan. He charged the "American Colleges of Physicians and Surgeons," and others, had been sending funds to British groups fighting the national health scheme, these funds going to the British Fellowship of Freedom in Medicine.

The American College of Physicians, in accordance with its Constitution and By-Laws, has restricted its activities wholly to scientific and educational affairs, and has made no contributions of any nature to the British Fellowship of Freedom in Medicine, or to any other organization at home or abroad dealing with nationalized or economic medicine.

A.C.P. Postgraduate Courses, Spring and Summer, 1950

For detailed outlines and registration forms consult E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Course No. 1, Clinical Allergy: Roosevelt Hospital, New York, N. Y., Robert A. Cooke, M.D., F.A.C.P., Director; 2 weeks, February 6–17; fee—Members, $120.00; Non-members, $240.00.

Course No. 2, Diseases of the Blood Vessels: Cornell University Medical College and New York Hospital, New York, N. Y., Irving S. Wright, M.D., F.A.C.P., Director; 1 week, March 13–18; fee—Members, $30.00; Non-members, $60.00.

Course No. 3, Recent Developments in the Cardiovascular Field: Michael Reese Hospital, Chicago, Ill., Louis N. Katz, M.D., F.A.C.P., Director; 1 week, March 20–25; fee—Members, $30.00; Non-members, $60.00.

Course No. 4, Electrocardiography: Basic Principles and Interpretation: Massachusetts General Hospital, Boston, Mass., Conger Williams, M.D., Director; 1 week, May 8–13; fee—Members, $50.00; Non-members, $120.00.

Course No. 5, Endocrinology: University of Illinois College of Medicine, Chicago, Ill., Willard O. Thompson, M.D., F.A.C.P., Director; 1 week, May 15–20; fee—Members, $30.00; Non-members, $60.00.

Course No. 6, The Dynamics of Metabolic Diseases: New York University Post-Graduate Medical School, New York, N. Y., Clarence E. de la Chapelle, M.D., F.A.C.P., Director, and Charles F. Wilkinson, Jr., M.D., Associate Director; 1 week, May 15–20; fee—Members, $30.00; Non-members, $60.00.

Course No. 7, Trends and Newer Developments in Internal Medicine: Temple University School of Medicine, Philadelphia, Pa., Thomas M. Durant, M.D., F.A.C.P., Director; 1 week, June 5–10; fee—Members, $30.00; Non-members, $60.00.

Course No. 8, INTERNAL MEDICINE: University of California Medical School, San Francisco, Calif., Stacy R. Mettier, M.D., F.A.C.P., Director; 1 week, June 19–23; fee—Members, $30.00; Non-members, $60.00.

Course No. 9, CLINICAL ASPECTS OF MALNUTRITION: Hospital de Enfermedades de la Nutrición, Mexico, D. F., Salvador Zubiran, M.D., F.A.C.P., Director; 2 weeks, August 14–26; fee—Members, $60.00; Non-members, $120.00.

A.C.P. REGIONAL MEETINGS

The following Regional Meetings of the American College of Physicians are scheduled or have been held since the beginning of 1950. Many others are under consideration and will be announced in due course.

EASTERN PENNSYLVANIA REGIONAL MEETING, Philadelphia, January 20, 1950, Thomas M. McMillan, F.A.C.P., Governor.

MANITOBA AND SASKATCHEWAN REGIONAL MEETING, Winnipeg, Man., February 10, 1950, C. H. A. Walton, F.A.C.P., Governor. Maurice C. Pincoffs, M.A.C.P., Baltimore, official representative from the Board of Regents.

NEBRASKA REGIONAL MEETING, Lincoln, Nebr., February 11, 1950, Joseph D. McCarthy, F.A.C.P., Governor. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the College, special guest speaker.

COLORADO REGIONAL MEETING, Denver, Colo., February 21, 1950, Ward Darley, F.A.C.P., Governor. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the College, special guest speaker.

MARYLAND-DISTRICT OF COLUMBIA REGIONAL MEETING, Baltimore, Md., February 25, 1950, Wetherbee Fort, F.A.C.P., Governor.

KANSAS REGIONAL MEETING, Topeka, Kans., March 17, 1950, William C. Menninger, F.A.C.P., Governor. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., special guest speaker from the Board of Regents.

NEW A.C.P. LIFE MEMBERS

The following Fellows have become Life Members of the American College of Physicians since the publication of the preceding issue of this journal. (Listed in order of subscription.)

Adolph R. Berger, New York, N. Y.
Robert A. Hare, Washington, D. C.
George W. Calver, Washington, D. C.
Alexander H. Colwell, Sr., Pittsburgh, Pa.
Ruel L. Alden, Hempstead, N. Y.
Turner Z. Cason, Jacksonville, Fla.
Walter A. Crist, West Collingswood, N. J.
Seymour H. Rinzler, New York, N. Y.
Herman M. Baker, Evansville, Ind.
Walter D. Ford, Detroit, Mich.
Isidore A. Feder, Brooklyn, N. Y.
Horace A. Anderson, Tacoma, Wash.
Ralph M. Watkins, Cleveland, Ohio
Frederick Lemere, Seattle, Wash.

A.C.P. Coöperates with CARE

The Board of Regents of the American College of Physicians on November 13, 1949, on recommendation of the Committee on Public Relations, approved a proposal that the College shall support in principle the program of the Coöperative for American Remittances to Europe, commonly known as "CARE." That program includes furnishing medical books and medical magazines to war-destroyed medical agencies overseas. Losses to universities, research institutions, libraries, museums and other agencies were staggering. Lost treasures cannot be replaced, but knowledge gained in the last decade can be shared by contributing through CARE books and publications to specific institutions.

The Board of Regents will send a number of free subscriptions for the ANNALS OF INTERNAL MEDICINE to libraries and medical schools selected by CARE. These institutions are located in Italy, Japan, Greece, Austria, Czechoslovakia, Korea, Finland, Norway and Germany. American doctors may channel their gifts through Mr. Milton L. Smith, Director of the Educational Unit, Coöperative for American Remittances to Europe, 50 Broad Street, New York 4, N. Y.

CERTIFYING BOARD EXAMINATIONS

American Board of Internal Medicine—William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison 3, Wis. Because of the large number of candidates now eligible for oral examination, the assignments have been made on a regional basis.

Chicago, Ill., February 8, 9, 10, 1950—Midwestern States from Ohio to the Dakotas and from Illinois to Louisiana.

Boston, Mass., April 13, 14, 15, 1950—Connecticut, Maine, Massachusetts, New Hampshire, New York, Rhode Island, Vermont.

San Francisco, Calif., June 21, 22, 23, 1950—Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Texas, Utah, Washington, Wyoming.

Place and date yet to be announced for Delaware, District of Columbia, Florida, Georgia, Maryland, New Jersey, North Carolina, Pennsylvania, South Carolina, Virginia and West Virginia.

Closing date for acceptance of applications is ten days after notification sent to eligible candidates.

American Board of Pediatrics—John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Oral examinations are scheduled as follows:

Richmond, Va., February 10, 11, 12, 1950.

Philadelphia, Pa., March 31, April 1, 2, 1950.

Cincinnati, Ohio, May 5, 6, 7, 1950.

San Francisco, Calif., June 30, July 1, 2, 1950.

THE JAMES ALEXANDER MILLER FELLOWSHIP FOR RESEARCH IN TUBERCULOSIS

The New York Tuberculosis and Health Association recently announced a research fellowship named for the late James Alexander Miller, who was a Master and Past President of the American College of Physicians, and a widely recognized authority in the field of tuberculosis. The fellowship will be available from July 1, 1950 to June 30, 1951. It is designed to support a qualified medical investigator who will devote full time to a research project with a definite bearing on tuberculosis. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the pursuit of the work. It is preferable that such laboratory or clinic be located in New York City. The stipend will be $5,000.

Application forms will be supplied on request to the above Association, 386 Fourth Avenue, New York 16, N. Y., and must be submitted in duplicate not later than March 1, 1950. Announcement of the award will be made during April, 1950.

National Gastro-Enterological Association 1950 Award Contest

One hundred dollars and a Certificate of Merit will be awarded by the National Gastro-Enterological Association for the best unpublished contribution on Gastro-enterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants must be members of the recognized national medical society of their countries. The winning contribution will be selected by a board of impartial judges and the award will be made at the Annual Convention Banquet of the Association in October, 1950. The Association reserves exclusive right of publication. Entries should be limited to 5,000 words, shall be typewritten in English, prepared in manuscript form, and submitted in five copies accompanied by an entry letter and must be received at the Association Headquarters, 1819 Broadway, New York 23, N. Y. not later than June 1, 1950.

American Association of Medical Clinics Organized

In Washington, D. C., on December 4 and 5, 1949, the American Association of Medical Clinics was organized as a non-profit association with the following purposes:

1. To elevate the standards of practice in medical clinics.
2. To foster and improve graduate medical education in such clinics.
3. To promote medical research in such clinics.
4. To give mutual help by the interchange of ideas and experiences of member clinics.

At the organization meeting 40 medical clinics throughout the United States and Puerto Rico were approved as charter members. Other clinics approved within the next 18 months will be called charter members. Any group of seven or more full-time physicians maintaining a private organization for the purpose of providing general medical care of high quality, according to the principles of ethics of the American Medical Association, shall be eligible, provided that five of the physicians practice five different major specialties, two of which shall be internal medicine and general surgery. The officers of the new association are: Dr. Wallace M. Yater, F.A.C.P., Yater Clinic, Washington, D. C., President; Dr. Clair L. Stealy, F.A.C.P., Rees-Stealy Clinic, San Diego, Calif., Vice President; Dr. Arthur H. Griep, Welborn Hospital Clinic, Evansville, Ind., Secretary-Treasurer.

Texas Academy of Internal Medicine Formed

The Texas Academy of Internal Medicine was recently organized and Dr. Samuel A. Shelburne, F.A.C.P., Dallas, was elected its first President. To be eligible, physicians must either be certified by the American Board of Internal Medicine or be a Fellow of the American College of Physicians. 175 physicians joined as charter members. The program of the Academy is almost completely in the field of clinical investigation along physiological and chemical lines. All meetings will be held at medical schools of the State of Texas and the program will be in charge of the Professor of Medicine, who has the privilege of drawing upon anyone in his school or elsewhere.

Dallas Southern Clinical Society

The Dallas Southern Clinical Society will hold its Nineteenth Annual Spring Clinical Conference, March 13–16, 1950, at Hotel Adolphus and the Baker Hotel. Sectional programs cover medicine, surgery, obstetrics-gynecology, pediatrics, urology, anesthesiology, eye, ear, nose and throat, and other sub-divisions. Dr. Ernest E. Irons, F.A.C.P., President of the American Medical Association, will be the special guest speaker at the Assembly the first evening. Registration fee for the entire Conference is $20.00. Programs available on request to the Headquarters of the Society, 433 Medical Arts Building, Dallas 1, Tex.

International Heart Congress, Paris, September 3–9, 1950

Dr. Paul D. White, F.A.C.P., Secretary pro tem of the International Cardiac Council, announces that titles and summaries (not exceeding 300 words) of papers offered for presentation at the First International Heart Congress in Paris should be sent to the Secretary of each applicant's national heart association throughout the world. A Committee of the American Heart Association has been established to select the most suitable communications from the U. S. A. to be forwarded to the Inter-American Cardiac Committee and thence to the headquarters in Paris, where final selection will be made. The listing submitted by the American Heart Association Committee will be arranged on a priority basis. It is anticipated that 400 to 500 papers may be read at the meeting in Paris, and that half of these will be allocated to the Western Hemisphere. Each communication is to take not over ten minutes as a rule, followed by a five-minute discussion period. For the United States, these titles and summaries should be in the hands of Dr. Charles A. R. Connor, Medical Director, American Heart Association, 1775 Broadway, New York City, by March 1.

Colonel Wesley C. Cox, F.A.C.P., Honored

Colonel Wesley C. Cox, F.A.C.P., (MC), USA, Chief of the Army Industrial Hygiene Laboratory at the Army Chemical Center, Maryland, was honored, December 14, 1949, by presentation of a diploma and gold medal in recognition of the best paper delivered before the First Inter-American Congress on Industrial Medicine. The presentation was made by General Juan Peron, President of the Argentine Republic. Colonel Cox, who is widely known as an authority on industrial health and hygiene, and is consultant in that field to Major General R. W. Bliss, Surgeon General of the Army, attended the Argentine meeting as the official representative of the Army and the American Association of Industrial Physicians and Surgeons.

At the Annual Meeting of the Philadelphia County Medical Society in January, Dr. Richard A. Kern, F.A.C.P., retired as President, being succeeded by Dr. Henry B. Kobler. Dr. Louis B. LaPlace, F.A.C.P., was named President-Elect and Dr. Malcolm W. Miller, F.A.C.P., was elected Secretary.

Dr. Cleon J. Gentzkow, F.A.C.P., retired Army Medical Corps colonel, has been appointed Director of the Pennsylvania State Health Department's Bureau of Laboratories at Philadelphia, succeeding the late Dr. A. P. Hitchens, F.A.C.P. Dr. Gentzkow will maintain offices in the Central Laboratory in the Hygiene Building of the University of Pennsylvania.

Dr. David I. Macht, F.A.C.P., formerly for many years lecturer in pharmacology, Johns Hopkins University, and now actively engaged as Research Physiologist and Pharmacologist in the Sinai Hospital, Baltimore, was presented with an honorary degree of Doctor of Theology, by the Ner Israel Rabbinical College of Baltimore, on the occasion of his fortieth anniversary as a research scientist and in recognition of his scientific contributions concerning biblical references to natural history, and his studies on the interrelationships of science and religion.

Dr. R. Finley Gayle, F.A.C.P., Richmond, Va., is now President of the Southern Psychiatric Association.

Dr. Kenneth M. Lynch, F.A.C.P., has been made President of the Medical College of the State of South Carolina. He has heretofore been Dean of the Medical College and Professor of Pathology.

Dr. George B. Dowling, F.A.C.P., formerly a member of the Medical Corps of the U. S. Navy, is now Medical Director and Assistant Manager of the southeastern area of the American Red Cross, Atlanta. He will have charge of the Red Cross blood program, nursing service, safety and nutrition services. Formerly Dr. Dowling was Deputy Administrator of the National Red Cross Blood Program.

Dr. Max M. Strumia, F.A.C.P., Philadelphia, President of the American Medical Relief for Italy, Assistant Professor of Pathology in the University of Pennsylvania Graduate School of Medicine, and Director of Laboratories at Bryn Mawr Hospital, during November, 1949, was presented with the Second Degree of the Star of Italian Solidarity for his assistance in the reconstruction of Italy.

Dr. Alonzo F. Brand, F.A.C.P., was recently appointed Regional Medical Director of the U. S. Public Health Service with headquarters in San Francisco. Dr. Brand will direct Public Health Service activities in California, Washington, Oregon, Arizona, Nevada, Alaska and Hawaii.

Dr. Cecil J. Watson, F.A.C.P., Professor of Medicine, University of Minnesota, delivered on January 27, 1950, the Third Annual Lecture in honor of Dr. Rudolph Matas, Emeritus Professor of Surgery, Tulane University of Louisiana School of Medicine, New Orleans. His subject was "Modern Concepts of Liver Function and Their Alteration in Disease."

Drs. Russell L. Cecil, F.A.C.P., New York, Chester M. Jones, F.A.C.P., Boston, George Morris Piersol, M.A.C.P., Philadelphia, and J. Burns Amberson, F.A.C.P., New York, were guest speakers at the Annual Assembly of the Medical Association of Puerto Rico, December 14–18, 1949.

Dr. Alex M. Burgess, F.A.C.P., Providence, R. I., has accepted a full-time appointment as section chief in medicine for the Veterans Administration in the New York-New England area. He will supervise the medical departments in about 30 veterans hospitals. He recently retired as chairman of the Department of Medicine at the Rhode Island Hospital. He is a Regent of the American College of Physicians and a member of the American Board of Internal Medicine.

OBITUARIES

DR. JOHN MUMFORD SWAN

John Mumford Swan, M.D., of Rochester, New York, a Fellow of the American College of Physicians since 1923, died on November 22, 1949, at the age of 79 years.

Dr. Swan was born in Newport, R. I., January 3, 1870; M.D., 1893, University of Pennsylvania School of Medicine; Demonstrator of Osteology and Assistant Demonstrator of Anatomy, University of Pennsylvania School of Medicine, 1894–1904; Instructor in Clinical Pathology and Tropical Medicine, Philadelphia Polyclinic Hospital, 1904–10; Associate Professor of Medicine, Medico-Chirurgical College of Philadelphia (dates not given but probably following the 1904 date at the University of Pennsylvania); later, Medical Director, Glen Springs Sanitarium; served during first World War and held rank of Colonel, Medical Reserve Corps, U. S. Army, for many years; formerly Executive Secretary, New York State Committee, American Society for the Control of Cancer; Staff Physician, Park Avenue Hospital, Rochester, N. Y., 1921 to about 1940; thereafter served as Consulting Physician, Park Avenue Hospital; retired from active work about 1947; in earlier years did postgraduate work at the London School of Tropical Medicine; member, Philadelphia County Medical Society, Pennsylvania State Medical Society, American Medical Association, Medical Society of the County of Monroe (N. Y.), Medical Society of the State of New York, College of Physicians of Philadelphia, Academy of Medicine of Rochester and American Climatological and Clinical Association; former Assistant Secretary, former Secretary and former President, American Society of Tropical Medicine; Life Member, Pathological Society of Philadelphia; former Associate Editor, New York Medical Journal; author of a great many published papers and several books, including "A Manual of Human Anatomy for First Year Students," "A Manual of Human Anatomy for Second Year Students," "Prescription Writing and Formulary" and "The History of the U. S. Army Base Hospital No. 19"; Diplomate, American Board of Internal Medicine.

In the death of Dr. Swan the medical profession of Rochester lost one of its valuable members. Dr. Swan was a very versatile man and in recent years was particularly active in the American Society for the Control of Cancer. He made many contributions to medical literature and he has presented to the College some very valuable and highly treasured books, one of which was a rare copy of the transactions of the John Guiteras Medical Society of Undergraduates—University of Pennsylvania, 1893, and another was an original manuscript prepared by himself on Jean Fernel.

EDWARD REIFENSTEIN, M.D.,
Governor for Western New York

DR. EDWIN CHARLES CORT

Edwin Charles Cort, M.D., D.Sc., F.A.C.P., F.A.C.S., died January 10, 1950, in the Alexandria Hospital, Alexandria, Virginia, a few months after he had been honorably retired by the Board of Foreign Missions of the Presbyterian Church in the U. S. A., following forty-one years of Christian medical service in Thailand.

Dr. Cort was born in Rochelle, Illinois, March 14, 1879, was graduated from Washington and Jefferson College, and received his M.D., from Johns Hopkins University School of Medicine in 1907. During succeeding years, he returned to Johns Hopkins on several occasions for postgraduate work. Shortly after his graduation in medicine, he accepted an appointment from the Board of Foreign Missions of the Presbyterian Church in the U. S. A., and was assigned to medical work in Lampang, Thailand. In those days of inadequate transportation, he covered most of the trails of northern Thailand on horseback in the line of his medical duties.

In 1915, he was assigned to the McCormick Hospital in Chiengmai, which was his chief interest until his retirement. The McCormick Hospital is now a thriving institution of high standard, which, in 1948, cared for 4,778 in-patients and 20,000 out-patients. On the staff are 8 doctors and 20 nurses and there are 100 student nurses in the training school. When Dr. Cort first took it over, the hospital was housed in makeshift barracks, and cared for 340 patients per year, with a death rate of 13 per cent.

In those days, plague, cholera, smallpox and famine provided horrible episodes against the background of constantly recurring malaria and dysentery. From 1910 to 1912, special emergencies took Dr. Cort to Lampang and to Prae, where the hospital had been closed for 8 years and a smallpox epidemic was raging. At Prae, he built a new hospital and rebuilt a girls' school.

During their 1915 furlough in the United States, Dr. and Mrs. Cort raised funds for a medical school, and on their return, Dr. Cort organized the Chiengmai Medical School affiliated with the Government University, serving as its Dean until 1919. Mrs. Cort had taken special courses in dietetics at Johns Hopkins University and devoted herself now to hospital diets, improving the eating habits of the common people, and the nurses' training program which was established in 1924.

In 1925, Dr. Cort became Superintendent of the McCormick Hospital, continuing also his medical teaching and practice. Much of his time was also given to the model Chiengmai Leper Asylum. Gifts from grateful patients were usually diverted to new equipment for the hospital. Dr. Cort served and was the friend of the royal family—also of the poorest peasant.

Leaving Thailand ahead of the Japanese invasion in 1941, he spent three years in Fatehgarh, India, where he is credited with having raised funds for a maternity ward, three child health centers and a nurses' dormitory, while running a mission hospital and building up a nurses' training school.

The Corts returned to Thailand from the United States at the earliest opportunity after World War II, April, 1946, taking with them drugs worth millions of ticals at the black market prices then prevailing. Malaria was rampant and since farmers had not had money to buy drugs, it seemed they would not have strength to harvest the rice crop. Enlisting the help of government health agencies and doctors and nurses, whom he had trained through long years of service, Dr. Cort set up channels for immediate, efficient, and honest distribution of atabrine. 350,000 individuals received treatment, recovered from their malaria and harvested the precious crops.

Also Dr. Cort, following the war, took back from the government and reëstablished seven mission hospitals in various regions of Thailand, and established the new Bangkok Christian Hospital. That Hospital was completed and dedicated on December 3, 1949.

On their return to the United States, following retirement, the Corts were entertained by ambassadors, cabinet members and royalty. Because they refused to accept gifts from colleagues and friends and patients, the E. C. Cort Memorial Fund for medical work in Thailand was established in their honor.

Dr. Cort wrote, edited and translated many treatises on tropical diseases. He was a Fellow (1933) of the American College of Physicians, the American College of Surgeons and of the Royal Society of Tropical Medicine (England).

Dr. Cort was venerated and loved by the common people of Thailand. He was recognized by many government honors including the Knight of the Order of the Crown and the Most Exalted Order of the White Elephant, bestowed upon him by the King.

DR. WILLIAM HENRY WATTERS

Dr. William Henry Watters, a Fellow of the College, died October 11, 1949, at the age of 73 of coronary thrombosis. He was born June 23, 1876, in Mechanics Falls, Maine, and obtained his A.B., A.M., and Ph.D. from McGill University in Montreal, Quebec. In 1900, he received his medical degree from Boston University School of Medicine. Shortly after graduating from medical school he registered for post-graduate work at the University of Glasgow and spent many pleasant hours under the direction of Sir Robert Muir. He was one of the first American physicians to do graduate work in Birmingham University at the time the Owens Medical College was merged with the University. During this period he had a temporary appointment as Instructor in Clinical Pathology under Professor Muir. When Dr. Watters returned to the United States he became Professor of Pathology at Boston University and held this post from 1903 to 1925, when he became Professor of Preventive Medicine for a period of ten years. His interest in medicine was very broad indeed and he always stressed pathology and internal medicine. He was a member of many medical societies and a consulting physician to a number of hospitals, including the following: Certified by the American Board of Internal Medicine; Fellow of the American College of Physicians; Medical Director, Boston-Miami Clinic; past President of the Massachusetts Medico-Legal Society; member of the International Association of Medical Museums and the Massachusetts Surgical and Gynecological Society; Associate Medical Examiner of Suffolk County; Consulting Physician, St. Francis Hospital, Miami Beach, Fla., and Cape Cod Hospital; at one time, Consulting Pathologist, Massachusetts Memorial Hospitals.

Dr. Watters had many friends and remained very active until the time of his death which was sudden. Only a few days before he died he attended meetings and dined with one of Professor Muir's colleagues, the present Regius Professor of Medicine of the University of Glasgow, Dr. John W. McNee. His friends will always remember him for his interest in medicine and pathology and he will be missed greatly by his colleagues and his patients.

Chester S. Keefer, M.D., F.A.C.P.,
Governor for Massachusetts

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Thirty-first Annual Session

BOSTON, MASS.

April 17–21, 1950

GENERAL SESSIONS AND LECTURES

Reginald Fitz, Boston, Mass., President

GENERAL CHAIRMAN

Chester S. Keefer, Boston, Mass.

COMMITTEE ON ARRANGEMENTS

Chester S. Keefer, Chairman

Theodore L. Badger
John F. Conlin
Lewis Dexter
Francis C. Lowell
Joseph F. Ross
Richard P. Stetson

Mrs. George W. Thorn

COMMITTEE ON AUDITORIUM

Theodore L. Badger, Chairman

Charles S. Davidson
John R. Graham
James A. Halsted
Stanley Kimball
Carey M. Peters
John P. Rattigan
Albert O. Seeler
Louis A. Sieracki
Thomas A. Warthin
Winthrop Wetherbee, Jr.

COMMITTEE ON CLINICS

Lewis Dexter, Chairman

Theodore B. Bayles, Robert Breck Brigham Hospital
Herrman L. Blumgart, Beth Israel Hospital
C. Sidney Burwell, Peter Bent Brigham Hospital
Laurence B. Ellis, Boston City Hospital
John Foley, Boston City Hospital
Lewis M. Hurxthal, Lahey Clinic
Charles Janeway, Children's Hospital
Alexander Marble, New England Deaconess Hospital
James H. Means, Massachusetts General Hospital
William C. Moloney, Boston City Hospital
Samuel Proger, New England Center Hospital
Maurice B. Strauss, Veterans Administration Hospital, Framingham
George W. Thorn, Peter Bent Brigham Hospital
Thomas A. Warthin, Veterans Administration Hospital, West Roxbury
Louis Weinstein, Haynes Memorial, Massachusetts Memorial Hospitals
Robert W. Wilkins, Massachusetts Memorial Hospitals

TELEVISED CLINICS

Ellsworth T. Neumann, Massachusetts General Hospital

COMMITTEE ON ENTERTAINMENT

Richard P. Stetson, Chairman

F. Dennette Adams
Frank N. Allan
Walter S. Burrage
C. Sidney Burwell
Maurice Fremont-Smith
Francis C. Hall
James A. Halsted
Albert A. Hornor
Hugh R. Leavell
Robert T. Monroe
Helen S. Pittman
Benjamin H. Ragle
Howard F. Root
Charles L. Short
Howard B. Sprague
Conrad Wesselhoeft

COMMITTEE ON TRANSPORTATION AND HOTELS

Francis C. Lowell, Chairman

Walter S. Burrage
Earle M. Chapman
Greene FitzHugh
Robert P. McCombs
Robert S. Palmer

COMMITTEE ON PANEL DISCUSSIONS

Joseph F. Ross, Chairman

Edwin B. Astwood
Henry J. Bakst
Elmer C. Bartels
Walter Bauer
Charles H. Burnett
Maxwell Finland
Seymour J. Gray
T. Hale Ham
Albert A. Hornor
Samuel A. Levine
W. Richard Ohler
Francis M. Rackemann

COMMITTEE ON PUBLICITY

John F. Conlin, Chairman

Dale G. Friend
Joseph Garland
Kermit H. Katz
James H. Townsend

COMMITTEE ON TECHNICAL EXHIBITS

George Morris Piersol, Chairman

Thomas Klein
Charles C. Wolferth

COMMITTEE ON LADIES' ENTERTAINMENT

Mrs. Reginald Fitz, Honorary Chairman
Mrs. George W. Thorn, Chairman

Mrs. Theodore L. Badger
Mrs. Walter S. Burrage
Mrs. C. Sidney Burwell
Mrs. James M. Faulkner
Mrs. Albert A. Hornor
Mrs. Chester S. Keefer
Mrs. Roger I. Lee
Mrs. George R. Minot
Mrs. Howard F. Root
Mrs. Howard B. Sprague
Mrs. Wintrop Wetherbee, Jr.

INVITATION

The historic city of Boston extends a warm welcome to the members and guests of The American College of Physicians' Annual Session to be held April 17–21, 1950. Centrally located in the downtown area the Hotel Statler will once again be the Headquarters Hotel. Within a short distance of the hotel is Mechanics' Hall, New England's largest auditorium, where general sessions and panel discussions are to be held. The same building will also house the technical exhibits.

The growth of the city of Boston since its founding in the year 1630 is the story of our country's rise to the eminent position it now holds in the world. History has commonly referred to old Boston as the CRADLE OF LIBERTY. The many landmarks, such as Bunker Hill, The Old North Church, Faneuil Hall, and Old Ironsides, are but a few of the monuments which all America treasures. Burial grounds of famous patriots and the memorable battlefields of Lexington and Concord have a strong appeal to all Americans. Here was fired the shot heard "round the world" giving notice that a new world of freethinking peoples was born. Plymouth Rock, a short distance from Boston, remains a symbol of our early settlers. All these and many more historic points of interest yearly attract thousands of visitors from all parts of the world. A special event for this year's Session to view will be one of Boston's great holidays of the year. A direct descendant of Paul Revere, attired in traditional garb, will ride a horse over the identical route which his ancestral parent followed that historic night in 1775.

Yet surrounded as they are by these milestones of America's history, the modern Bostonian is more apt to remind his vistors that Boston is one of the world's leading educational and research centers. From the banks of the Charles River one can see at a glance Harvard University, Boston University, and the Massachusetts Institute of Technology. Important atomic research is being carried on at these institutions. Within a short distance on the lower banks of the river stands the Massachusetts General Hospital. Under its pretentious Bulfinch Dome the first public demonstration of ether as an anesthetic was held in the year 1846. Boston medical schools lie within close proximity of each other and the major hospital area.

Harvard Medical School is adjacent to the Children's Hospital, the Peter Bent Brigham Hospital, Boston Lying-In Hospital, and Beth Israel Hospital. Nearby is the Good Samaritan Hospital, famed for its research and treatment of rheumatic fever. The Children's Medical Center is recognized as a leading institution in the study and care of child diseases. Tufts College Medical School and Boston University School of Medicine are conveniently located in the areas of the New England Center Hospital, Boston City Hospital and the Massachusetts Memorial Hospitals. The Lahey Clinic and the Pratt Diagnostic Clinic will be of interest to attending Fellows and their guests.

The Hub city of New England is commonly known as the biggest little city in our country with an approximate population of 800,000. Yet, if the surrounding metropolitan area were to be included, it would be among the nation's largest cities in area. The leading industries are wool, textiles, leather, shoes, paper and printing. It is among the world's leaders in the fishing industry. Along with being the gateway to one of the nation's great vacation and recreational areas it has long maintained a status as an insurance and financial center. Recent developments show a surge of construction, and the new John Hancock Mutual Insurance Company Building will attract the eye of any visitor. It is the tallest building in North America beyond New York City.

Boston's museums, colleges, libraries and scenic drives will make any visitor's stay more pleasant. In a matter of minutes one can travel from the downtown area to the Logan International Airport, visit the scene of the Boston Tea Party, and see

FIG. 1. Aerial view of downtown Boston overlooking the Charles River and Boston Harbor.

FIG. 2. Aerial view of Copley Square, Boston, Mass. Boston Public Library in the foreground.

the entire Boston waterfront. The students of drama and music will find many congenial activities. The gourmet will long remember the quaint atmosphere and delicacies of Boston's renowned eating places.

A cordial welcome and traditional New England hospitality await your visit to one of the nation's oldest cities.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Mechanics' Building

111 Huntington Avenue

Registration headquarters, the information bureau, technical exhibits, general sessions, morning lectures, panel discussions, televised clinics and clinic conferences, meetings of committees, of the Board of Regents and of the Board of Governors. The Annual Convocation and the Annual Banquet will take place in the Grand Ballroom of the Hotel Statler.

HOTEL ACCOMMODATIONS

A fully adequate number of first-class guest rooms has been reserved in close proximity to Mechanics' Building, and a Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at the Boston Convention Bureau, 80 Federal Street, Boston 10, Mass. Applications for rooms should be made to this Bureau, preferably on the official form provided by the College, but in the absence of the form, the Housing Bureau will handle letters of application, provided the applicant identifies himself with the College and its Annual Session. It is requested that five choices of hotels be indicated, and that a reasonable range of rates be shown. Whenever possible arrangements should be made for occupancy of rooms accommodating two persons. Confirmation from the hotel where the reservation has been made will be mailed to each applicant. If, after making reservations, the applicant finds it impossible to attend, he is requested to notify the Housing Bureau promptly so that his accommodations may be made available to another physician.

LIST OF HOTELS

Hotel	Type of Room and Rate	
STATLER (*3 blocks)	60 singles	$ 4.00 to $10.00
Park Square	200 doubles	6.50 to 12.50
	25 twins	9.50 to 14.00
	7 suites	17.00 to 27.50
BELLEVUE (*7 blocks)	25 doubles	$ 6.00 to $ 8.50
21 Beacon Street	25 twins	7.50 to 11.00
	25 suites	12.00 to 15.00
BRADFORD (*5 blocks)	65 doubles	$ 6.00 to $ 8.00
275 Tremont Street	50 twins	6.50 to 8.50
	5 suites	12.00 to 14.00
BRAEMORE (*1 mile)	20 twins	$ 7.00 to $ 9.50
464 Commonwealth Avenue	6 suites	10.00 to 15.00
BUCKMINSTER (*8 blocks)	10 singles	$ 3.50 to $ 5.50
645 Beacon Street	25 doubles	5.00 to 6.50
	25 twins	5.00 to 6.50

* Indicates distance from MECHANICS' BUILDING.

COMMANDER (*3 miles) 16 Garden Street, Cambridge	50 twins	$ 7.50 to $ 9.00
	10 doubles	7.00 to 9.00
CONTINENTAL (*3 miles) 25 Garden Street, Cambridge	10 doubles	$ 6.00 to $ 7.00
	10 twins	7.00 to 8.00
COPLEY PLAZA (*2 blocks) Copley Square	25 singles	$ 5.00 to $ 7.70
	60 doubles	7.70 to 9.90
	60 twins	8.80 to 14.00
	5 suites	15.00 to 25.00
COPLEY SQUARE (*1 block) 47 Huntington Avenue	10 singles	$ 4.00 to $ 5.00
	10 doubles	6.00
	10 twins	7.00
	5 suites	10.00 to 14.00
ESSEX (*15 blocks) South Station	20 singles	$ 2.50 to $ 5.00
	30 doubles	5.50 to 7.00
	40 twins	5.50 to 7.00
FENSGATE (*7 blocks) 534 Beacon Street	5 singles	$ 5.00 to $12.00
	25 twins	8.00 to 15.00
GARDNER (*2 blocks) 199 Massachusetts Avenue	10 doubles	4.50 to $ 6.00
	10 twins	5.00 to 6.50
	2 suites	10.50 to 12.00
HAMPTON COURT (*1 mile) 1223 Beacon Street, Brookline	5 suites	$10.00 to $20.00
HEMENWAY (*3 blocks) 91 Westland Avenue	20 doubles	$ 5.00 to $ 5.50
KENMORE (*1 mile) Kenmore Square	5 singles	$ 4.50 to $ 8.00
	10 doubles	7.00 to 11.00
	40 twins	7.50 to 12.00
	6 suites	12.00 to 16.00
LENOX (*2 blocks) Exeter Street	5 singles	$ 4.00 to $ 5.00
	10 doubles	6.00 to 8.00
	10 twins	8.00
	8 suites	10.00 to 16.00
LINCOLNSHIRE 20 Charles Street	10 twins	$ 8.00 to $10.00
	3 suites	10.00 to 20.00
MANGER (*2 miles) North Station	10 singles	$ 3.85 to $ 5.50
	75 doubles	5.00 to 7.50
	50 twins	6.00 to 8.00
MINERVA (*1 block) 214 Huntington Avenue	5 singles	$ 3.00 to $ 5.00
	8 doubles	4.00 to 5.00
	4 twins	5.50 to 6.50
PARKER HOUSE (*6 blocks) 60 School Street	50 singles	$ 4.00 to $ 7.00
	125 doubles	6.50 to 9.00
	75 twins	8.00 to 12.00
	3 suites	14.00 to 16.00
PURITAN (*1 mile) 390 Commonwealth Avenue	10 twins	$ 7.50 to $ 9.50
	6 suites	12.00 to 19.50
RITZ-CARLTON (*3 blocks) 15 Arlington Street	5 twins	$12.00 to $13.50
	20 suites	12.00 to 36.00
SHERATON (*1 mile) 91 Bay State Road	15 twins	$ 8.00 to $12.00
	15 suites	10.00 to 25.00
SOMERSET (*1 mile) 400 Commonwealth Avenue	15 twins	$ 9.00 to $11.00
	20 suites	12.00 to 25.00

TOURAINE (*5 blocks)	20 singles	$ 4.50 to $ 6.00
62 Boylston Street	20 doubles	7.00 to 9.50
	25 twins	7.50 to 9.50
	10 suites	16.00 to 18.00
VENDOME (*3 blocks)	5 doubles	$ 5.50 to $ 8.75
160 Commonwealth Avenue	10 twins	6.50 to 8.75

Who May Register—

(*a*) All members of The American College of Physicians in good standing for 1950.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses at medical schools in Greater Boston, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions and morning lectures.

(*d*) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions and morning lectures.

(*e*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States or Canada, without registration fee, **upon presentation of proper credentials.**

(*f*) Qualified physicians who may wish to attend this Session as visitors, sponsored by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

Registration Bureau—While official registration will start on Monday morning, April 17, advance registration of members and exhibitors will be provided for on Sunday, April 16, from 2:30 to 5:00 in the afternoon. The Registration Bureau, located by the Main Entrance of Mechanics' Building, will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for all Clinics, Clinico-Pathological Conferences and Panel Discussions will be sent with the individual program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at the Mechanics' Building.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held from 2:00 to 2:40 P.M., Thursday, April 20, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer, and the presentation of certain amendments to the Constitution and By-Laws. The President-Elect, Dr. William S. Middleton, Madison, Wisconsin, will be inducted into office.

Board and Committee Meetings—All meetings will be held at Mechanics' Building, Second Floor. Special meetings will be announced and posted.

A Dinner Meeting of the Board of Regents and of the Board of Governors will be held at the Harvard Club, Sunday, April 16, 7:00 P.M.

Committee on Credentials

Saturday, April 15, 10:00 A.M., Executive Secretary's Office, Mechanics' Building.

Joint Meeting: Board of Regents and Board of Governors

Sunday, April 16, 2:00 P.M., Paul Revere Reception Hall, Mechanics' Building, Second Floor.

Board of Regents

Tuesday, April 18, 12:00 M., Paul Revere Reception Hall, Mechanics' Building, Second Floor.*

Friday, April 21, 12:00 M., Paul Revere Reception Hall, Mechanics' Building, Second Floor.*

Board of Governors

Wednesday, April 19, 12:00 M., Paul Revere Reception Hall, Mechanics' Building, Second Floor.*

Other Committee meetings will be announced in the formal program and also posted on the Bulletin Boards at the Statler Hotel and the Mechanics' Building.

SPECIAL FEATURES

Special Trains—No official arrangements have been concluded for complete special trains, but, in some localities in the West, the College Governors may sponsor special cars on certain trains to Boston and return. Members are advised to consult the Governors for their states concerning any special car or travel arrangements.

Post-Convention Cruise to Bermuda—The early date of the Annual Session of the College in Boston makes it impractical to arrange a post-convention activity in New England; consequently, and partially due to the fact that many were unable to participate in the post-convention cruise to Bermuda after the 1949 Annual Session in New York, another such cruise is planned this year. To many, Bermuda is a vacation paradise, continuously attractive regardless of how many times the island has been visited before. The superior accommodations and appointments of the *Queen of Bermuda* offers a total of four days of rest at sea, with about two and one-half days in Bermuda amid a galaxy of flowers and rolling coral hills. The cruise will be under the direction of Mr. Leon V. Arnold, Travel Consultant, 36 Washington Square, West, New York 11, N. Y. The number of accommodations is somewhat limited and members are urged to communicate immediately with Mr. Arnold to secure plans of the ship, to select staterooms and to complete reservations.

A late afternoon train from Boston gives the night and Saturday morning in New York for personal affairs; or one may leave Boston on Saturday morning and arrive in New York in time for sailing at 3:00 P.M. Sunday, April 23, is spent at sea, with arrival in Bermuda on Monday, April 24. Return sailing from Hamilton, Bermuda, at 3:00 P.M., April 26, arriving in New York at 9:00 A.M., April 28. In most cases, members living east of the Mississippi, may keep office appointments by Saturday, April 29.

Auld Lang Syne and Greeting Hour—Monday, April 17, 5:00 to 7:00 P.M.; Sandwich Supper, 6:30 to 8:00 P.M.—The combined men's and women's Committees on Entertainment have arranged an informal Cocktail Party and Sandwich Supper on Monday evening, 5:00 to 8:00, in the Georgian Room of the Hotel Statler. During this period of sociability it is hoped that the officers and members with their wives will form a Mutual Reception Committee to renew old acquaintances and to meet and greet our newer members. Tickets available at the Registration Bureau in

* Buffet luncheon served.

Mechanics' Hall and at the Ladies' Registration Headquarters in the Hotel Statler. Since this feature occurs the first evening of the Session, it is urgently requested that the advance reservation card be filled out and mailed to the Executive Secretary, 4200 Pine St., Philadelphia 4, Pa., on or before April 10, in order that proper accommodations are engaged. Tickets may be paid for and picked up by 2:00 P.M., Monday, at the Registration Desk, Mechanics' Building. Price, $3.50.

Symphony Concert, Monday, April 17, 8:45 P.M.—Again, as in 1941, the kindly efforts of Dr. Roger I. Lee playing a leading rôle, the College is privileged to attend a concert given for it by the Boston Symphony Orchestra under the leadership of its new conductor, Mr. Charles Munch. All who were present at the former symphony concert in Boston recall with lasting pleasure the delights of that evening's entertainment and, under the inspirational leadership of Mr. Munch, this evening promises to be one long to be remembered by the College. Existing regulations make impossible an outright gift of the Hall or of the Orchestra for the evening, but the Conductor, in donating his services, has done us an inestimable favor in return for which a capacity audience is our earnest hope. Use the reservation card, accompanying the final program, addressed to Charles L. Short, M.D., 264 Beacon St., Boston, Mass., for advance reservations, filing same by or before April 10. Tickets must be paid for and picked up at the Registration Desk at Mechanics' Building before 2:00 P.M., April 17, at which time remaining unassigned tickets, if any, will be disposed of "first come, first serve." Price, Orchestra Floor and First Balcony, $3.00 each; Second Balcony, $2.00 each.

The Annual Convocation and the President's Reception, Wednesday, April 19—The Annual Convocation of the College will be held at 8:30 P.M., April 19, in the Ballroom of the Hotel Statler. All members of the College and their families, and those of the public who are interested, are cordially invited. No tickets are required. All physicians elected Fellows of the College since the 1949 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents and Governors are requested to assemble in Parlor A, Mezzanine Floor; and new Fellows to be inducted to assemble in the Georgian Room, Mezzanine Floor, Hotel Statler, at 7:45 P.M., preparatory to the formation of the procession.

The Convocation ceremony will include the President's address, "The Individuality of The American College of Physicians," and the Convocational Oration, "The Royal College of Physicians," by Lord Moran, of London, England, President of the Royal College of Physicians. The John Phillips Memorial Medal for 1950, the James D. Bruce Memorial Medal for 1950 and the Alfred Stengel Diploma for 1950 will be awarded. Recipients of Research Fellowships and of Latin-American Fellowships of the College for 1950 will be announced, and a Mastership will be conferred upon a distinguished member of the College. The class of new Fellows will be inducted by the President.

Following the Convocation, the President's Reception will be held in the Georgian Room, after which the dance will take place in the Grand Ballroom.

The Annual Banquet, Thursday, April 20—Before the Banquet, a "Dutch Treat" Cocktail Party will be held in the Ballroom Assembly at 7:00 P.M. Fellows and their guests are urged to attend this gathering preparatory to the more formal ceremony to follow.

The Banquet will be held in the Ballroom of the Hotel Statler at 8:00 P.M. A musical program will precede the introduction of the speaker, Dr. James Bryant Conant, President of Harvard University, whose title will be announced in the subsequent program. Table reservations for groups may be arranged. Tickets should be obtained at the Registration Bureau by 5:00 P.M., Wednesday, to enable adequate preparations by your committee. Price, $8.00 per person.

Other General Entertainment Features

Tuesday Evening, April 18—Tuesday evening will be a free evening—open for private dinner parties, theaters, and other entertainment. A list of theaters with prices will be published with the subsequent program and those wishing reservations should make prompt application to Mr. Cliff Edwards, Hotel Statler. A charge of sixty cents in addition to the ticket price will be made.

The Ladies' Entertainment Committee has arranged entree for the members and their guests to a service in the historic Old North Church at 8:00 P.M. This is "The Hanging of the Lantern," held yearly on the anniversary of the midnight ride of Paul Revere. The opportunity to visit this historic shrine of American liberty is one greatly appreciated, and those interested should apply promptly at the time of registration as the capacity of the Church is limited. Transportation to and from Hotel Statler may be obtained if desired.

Entertainment of Visiting Women—The Ladies' Entertainment Committee has prepared the following program to welcome to Boston the wives of the members of The American College of Physicians, hoping that they will enjoy their visit and take away with them pleasant memories of their stay. Those arriving early may register Sunday afternoon, April 16, from 2:00 to 5:00 P.M. on the Mezzanine Floor of the Hotel Statler. Registration will continue Monday through Thursday from 9:00 A.M. to 5:00 P.M.

Certain of the entertainment features are limited in accommodations and, therefore, early registration for each event is essential.

Monday, April 17

9:00 A.M. to 5:00 P.M., Registration on the Mezzanine Floor of the Hotel Statler.

5:00 P.M. to 8:00 P.M., Cocktail party and Sandwich Supper for members and their wives in the Georgian Room of the Hotel Statler. Tickets, $3.50.

8:45 P. M. to 10:30 P.M.—Concert by the Boston Symphony Orchestra, Mr. Charles Munch, Conductor. Symphony Hall. Price of tickets, $3.00 orchestra and first balcony; $2.00 second balcony.

Tuesday, April 18

11:00 A.M. Optional trip to the Isabella Gardner Museum at Fenway Park.

12:30 P.M. Luncheon and Fashion Show—Somerset Hotel. $4.50.

8:00 P.M. "The Hanging of the Lanterns" service at the Old North Church, held annually on the eve of the "Midnight Ride of Paul Revere."

Wednesday, April 19

10:00 A.M. 175th anniversary celebration of the Battles of Concord and Lexington. Buses will leave Hotel Statler at 10:00 A.M. and return about 2:00 P.M. Luncheon at extra cost may be procured in Concord. Tickets, $3.00.

4:00 P.M. Reception Tea at the Museum of Fine Arts in the Tapestry Room, as guests of the Women's Committee. Buses will leave Hotel Statler at 3:15 P.M. Fare, $.70.

8:30 P.M. Convocation, followed by President's Reception and Dance, Ballroom, Hotel Statler.

Thursday, April 20

10:30 A.M. Historic Boston—Paul Revere House, Old and New State Houses, Boston Common, Bunker Hill Monument, Navy Yard (Frigate Constitution), Beacon Hill. Tickets, $1.75.

2:00 P.M. Famous Universities—Harvard University, glass flowers, Memorial Chapel, Widener Library, Harvard Yard, Harvard Medical School. Massachusetts Institute of Technology. Boston University. Tufts College. Tickets, $1.75.

7:00 P.M. "Dutch Treat" Cocktail Party, Assembly Room, Mezzanine, Hotel Statler.

8:00 P.M. Annual Banquet of the College in the Ballroom of Hotel Statler.

THE TECHNICAL EXHIBIT

The Technical Exhibit will be located on the Main Floor of Mechanics' Building and will be one of the most attractive and all-inclusive exhibits ever conducted by the College. The Committee on Exhibits maintains the highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant exhibits are eliminated and only firms which present a group of approved products of scientific interest to the internist and allied specialist may exhibit.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention, thus recognizing their contributions to the meeting and the effort they make and the expense to which they go in building superior displays and furnishing, freely, valuable information.

The Exhibits will be open from 8:30 A.M. to 5:45 P.M. daily from Monday through Thursday, and from 8:30 A.M. to 2:30 P.M. on Friday. Intermissions have been arranged providing additional time for the inspection of Exhibits.

1950 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
Almay, Division of Schieffelin & Co., New York, N. Y.
American Hospital Supply Corporation, Evanston, Ill.
Ames Company, Inc., Elkhart, Ind.
Appleton-Century-Crofts, Inc., New York, N. Y.
Arlington Chemical Company, The, Yonkers, N. Y.
Armour Laboratories, The, Chicago, Ill.
Associated Medical Care Plans, Chicago, Ill.
Association of American University Presses, Chicago, Ill.
Ayerst, McKenna & Harrison, Limited, New York, N. Y.

Baum Co., Inc., W. A., New York, N. Y.
Becton, Dickinson & Co., Rutherford, N. J.
Bilhuber-Knoll Corp., Orange, N. J.
Bischoff Company, Inc., Ernst, Ivoryton, Conn.
Blakiston Company, The, Philadelphia, Pa.
Bristol Laboratories Inc., Syracuse, N. Y.
Burroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y.

Cambridge Instrument Co., Inc., New York, N. Y.
Cameron Surgical Specialty Company, Chicago, Ill., and New York, N. Y.
Carnation Company, Los Angeles, Calif.
Chilcott Laboratories—The Maltine Company, Morris Plains, N. J.
Chilean Iodine Educational Bureau, Inc., New York, N. Y.
Ciba Pharmaceutical Products, Inc., Summit, N. J.
Collins, Inc., Warren E., Boston, Mass.
Commercial Solvents Corporation, New York, N. Y.

Davies, Rose & Company, Limited, Boston, Mass.
Davis Company, F. A., Philadelphia, Pa.

Devereux Schools, Devon, Pa., and Santa Barbara, Calif.
DeVilbiss Company, The, Toledo, Ohio
Dietene Company, The, Minneapolis, Minn.
Doak Company, Inc., Cleveland, Ohio
Doho Chemical Corporation, New York, N. Y.
Duke Laboratories, Inc., Stamford, Conn.

Emerson Co., J. H., Cambridge, Mass.

Fleet Co., Inc., C. B., Lynchburg, Va.
Flint, Eaton & Company, Decatur, Ill.

General Electric X-Ray Corporation, Milwaukee, Wis.
Gerber Products Company, Fremont, Mich.
Gradwohl Laboratories, St. Louis, Mo.
Grune & Stratton, Inc., New York, N. Y.

Hanovia Chemical & Manufacturing Company, Newark, N. J.
Harrower Laboratory, Inc., The, Jersey City, N. J., and St. Louis, Mo.
Heinz Company, H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hoffmann-La Roche, Inc., Nutley, N. J.
Hollister-Stier Laboratories, Wilkinsburg, Pa., Spokane, Wash., & Los Angeles, Calif.
Hospital Bedhight Company, Fort Worth, Tex.

Ives-Cameron Company, Inc., New York, N. Y.

Jones Metabolism Equipment Co., Chicago, Ill.
"Junket" Brand Foods Division, Chr. Hansen's Laboratory, Inc., Little Falls, N. Y.

Kelley-Koett Manufacturing Co., The, Covington, Ky.
Kellogg Company, Battle Creek, Mich.
Knox Gelatine Co., Inc., Charles B., Johnstown, N. Y.

Lakeside Laboratories, Inc., Milwaukee, Wis.
LaMotte Chemical Products Company, Towson, Md.
Lea & Febiger, Philadelphia, Pa.
Lederle Laboratories Division, American Cyanamid Company, New York, N. Y.
Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.

Macmillan Company, The, New York, N. Y.
Mallon Chemical Corporation, New York, N. Y.
Massengill Company, The S. E., Bristol, Tenn.
McNeil Laboratories, Inc., Philadelphia, Pa.
Mead Johnson & Company, Evansville, Ind.
Medical Bureau, The, Chicago, Ill.
Medical Film Guild, New York, N. Y.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.

National Drug Company, The, Philadelphia, Pa.
Nelson & Sons, Thomas, New York, N. Y.

Oxford University Press, Inc., New York, N. Y.

Parke, Davis & Company, Detroit, Mich.
Patch Company, The E. L., Stoneham, Mass.

Picker X-Ray Corporation, New York, N. Y.
Pitman-Moore Company, Indianapolis, Ind.

Reed & Carnrick, Jersey City, N. J.
Rystan Company, Inc., Mount Vernon, N. Y.

Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schering Corporation, Bloomfield, N. J.
Schieffelin & Co., New York, N. Y.
Searle & Co., G. D., Chicago, Ill.
Sharp & Dohme, Inc., Philadelphia, Pa.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.

Taylor Instrument Companies, Rochester, N. Y.
Technicon Cardiograph Corp., New York, N. Y.

U. M. A., Inc., New York, N. Y.
U. S. Vitamin Corporation, New York, N. Y.
Upjohn Company, The, Kalamazoo, Mich.

Varick Pharmacal Co., Inc., New York, N. Y.

Wallace & Tiernan Products, Inc., Belleville, N. J.
Westinghouse Electric Corporation, Pittsburgh, Pa.
White Laboratories, Inc., Newark, N. J.
Williams & Wilkins Company, The, Baltimore, Md.
Winthrop-Stearns, Inc., New York, N. Y.
Woodward Medical Personnel Bureau, Chicago, Ill.
Wyeth Incorporated, Philadelphia, Pa.

Year Book Publishers, Inc., The, Chicago, Ill.

GENERAL OUTLINE OF THE BOSTON SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 17	April 18	April 19	April 20	April 21
9:15 A.M. to 11:30 A.M.	Morning free. **Registration, Exhibits, etc.**	Hospital Clinics **Colored TV Clinic**	**Morning Lectures Colored TV Clinic**	Hospital Clinics **Colored TV Clinic**	**Morning Lectures Colored TV Clinic**
12:00 M. to 1:15 P.M.		**5 Panel Discussions** (1 at Hotel Copley Plaza)	**5 Panel Discussions** (1 at Hotel Copley Plaza)	**5 Panel Discussions** (1 at Hotel Copley Plaza)	**5 Panel Discussions** (1 at Hotel Copley Plaza)
2:00 P.M. to 5:00 P.M.	**1st General Session**	**2nd General Session**	**3rd General Session**	**Annual Business Meeting 4th General Session**	**5th General Session**
5:00 P.M. to 8:00 P.M.	Cocktail Party and Sandwich Supper—Hotel Statler				
EVENING	Entertainment — Symphony Concert Symphony Hall		7:45 Pre-Convocation Assembly 8:30 Convocation 10:15 President's Reception and Ball—Hotel Statler	7:00 "Dutch Treat" Cocktail Party 8:00 Banquet—Hotel Statler	

Boldface type indicates events at Mechanics' Building.

GENERAL SESSIONS PROGRAM

Grand Hall, Mechanics' Building

FIRST GENERAL SESSION

Monday Afternoon, April 17, 1950

Presiding Officer

Chester S. Keefer, F.A.C.P., Boston, General Chairman

P.M.

2:00 **Addresses of Welcome:**

The Honorable JOHN B. HYNES, Mayor of the City of Boston.
HOWARD M. JONES, LL.D., President, The American Academy of Arts and Sciences, Boston.
ALBERT A. HORNOR, F.A.C.P., Vice President, The Massachusetts Medical Society, Boston.
ALEXANDER J. A. CAMPBELL, F.A.C.S., President, The Suffolk District Medical Society, Boston.
DWIGHT O'HARA, F.A.C.P., Chairman, The Deans' Committee, Veterans Administration (Boston Area).

Response to Addresses of Welcome:

REGINALD FITZ, F.A.C.P., President, The American College of Physicians.

Presiding Officer

President Reginald Fitz, F.A.C.P., Boston

2:30 **The James D. Bruce Memorial Lecture on Preventive Medicine: Global Strategy in Preventive Medicine.**
KARL F. MEYER, M.D. (by invitation), Director, The George Williams Hooper Foundation, San Francisco.

3:15 INTERMISSION.

3:35 **The Industrial Aspects of Coronary Disease.**
GEORGE F. STRONG, F.A.C.P., Vancouver, B.C.

3:55 **The Changing Nature of Pneumonia.**
HOBART A. REIMANN, F.A.C.P., Professor of Medicine, The Jefferson Medical College of Philadelphia.

4:15 **Wear and Tear.**
LORD MORAN, F.R.C.P. (by invitation), President, The Royal College of Physicians, London, England.

4:35 **Radioactive Iodine in the Treatment of Angina Pectoris.**
HERRMAN L. BLUMGART, F.A.C.P., Professor of Medicine, Harvard University.

4:55 ADJOURNMENT.

SECOND GENERAL SESSION

Grand Hall, Mechanics' Building

Tuesday Afternoon, April 18, 1950

Presiding Officer

William S. Middleton, F.A.C.P., Madison, Wis.

P.M.

2:00 **Present-day Undesirable Trends in the Training of Physicians and Teachers of Medicine.**
HENRY A. CHRISTIAN, M.A.C.P., Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University.

2:25 **The Incidence of Hypertension in Puerto Rico.**
RAMÓN M. SUÁREZ, F.A.C.P., San Juan, Puerto Rico.

2:45 **The Treatment of Intractable Peptic Ulcer.**
WALTER L. PALMER, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine.

3:05 **A Study of the Movements and Sounds of the Heart Valves** (a motion picture and sound recording).
HARRY L. SMITH, F.A.C.P., Mayo Clinic, Rochester, Minn.

3:30 INTERMISSION.

3:50 **The Biochemistry of Multiple Sclerosis.**
HAROLD H. JONES, F.A.C.P., Winfield, Kans.

4:10 **The Present Status of the Etiology of Pernicious Anemia.**
WILLIAM B. CASTLE, F.A.C.P., Recipient of the John Phillips Memorial Award in 1933 for his studies on anemia, Professor of Medicine, Harvard University.

4:30 **Rocky Mountain Spotted Fever in Long Island.**
JOHN K. MILLER (Associate), Associate Director, Department of Health, State of New York, Albany.

4:55 ADJOURNMENT.

THIRD GENERAL SESSION

Grand Hall, Mechanics' Building

Wednesday Afternoon, April 19, 1950

Presiding Officer

Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.

P.M.

2:00 **The Abuse of the Prescription Pad.**
D. SCLATER LEWIS, F.A.C.P., President, Royal College of Physicians and Surgeons of Canada; Professor of Therapeutics, McGill University.

2:20 **The John Phillips Memorial Lecture: Cortisone.**
EDWARD C. KENDALL, Ph.D. (by invitation), Mayo Clinic, Rochester, Minn.

3:10 INTERMISSION.

3:30 **The Clinical Value of Liver Biopsy.**
LEON SCHIFF, F.A.C.P., Associate Professor of Medicine, University of Cincinnati.

3:50 **The Results of Splenectomy in Banti's Disease.**
ROBERT H. DURHAM, F.A.C.P., Physician-in-Charge, Division of General Medicine, Henry Ford Hospital, Detroit.

4:10 **Clinical Disorders of the Neurohypophysis.**
THOMAS P. FINDLEY, F.A.C.P., Ochsner Clinic, New Orleans.

4:30 **Present Role of the Artificial Kidney in Clinical Therapy.**
JOHN P. MERRILL (by invitation), Research Fellow in Medicine, Harvard University.

4:55 ADJOURNMENT.

FOURTH GENERAL SESSION

Grand Hall, Mechanics' Building

Thursday Afternoon, April 20, 1950

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; elections of of new Officers, Regents and Governors will take place; certain amendments to the Constitution and By-Laws will be presented; President-Elect William S. Middleton, of Madison, Wis., will be inducted at President and will make a brief inaugural address.

Presiding Officer

Hugh J. Morgan, F.A.C.P., Nashville, Tenn.

2:40 **Clinical Observations on Cortisone and ACTH in the Treatment of Rheumatic Diseases.**
PHILIP S. HENCH, F.A.C.P., Mayo Clinic, Rochester, Minn.

3:20 **The Effects of ACTH and Cortisone in Allergic Diseases.**
A. MCGEHEE HARVEY, F.A.C.P., Research Fellow of the College in 1937, Professor of Medicine, Johns Hopkins University.

3:40 **The Physiological Effects of ACTH and Cortisone.**
GEORGE W. THORN, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University.

4:00 INTERMISSION.

4:15 **The Experiences of a Teacher of Medicine for Forty Years.**
JAMES E. PAULLIN, M.A.C.P., Professor of Clinical Medicine, Emory University.

4:35 **The Problem of Intractable Heart Failure.**
SAMUEL H. PROGER (by invitation), Professor of Medicine, Tufts College School of Medicine.

4:55 **Chronic Barbiturate Intoxication** (with motion picture demonstration).
HARRIS ISBELL (Associate), Director of Research, Public Health Service Hospital, Lexington, Ky.

5:15 ADJOURNMENT.

FIFTH GENERAL SESSION

Grand Hall, Mechanics' Building

Friday Afternoon, April 21, 1950

Presiding Officer

Edward L. Bortz, F.A.C.P., Philadelphia, Pa.

P.M.

2:00 **The Internist's Number One Problem** (Chronic Disease in an Aging Population).
HOWARD A. RUSK, F.A.C.P., Professor of Rehabilitation and Physical Medicine, New York University.

2:20 **The Successes and Disappointments in Intravenous Diagnosis and Therapy.**
ROGER I. LEE, F.A.C.P., Fellow of Harvard College.

2:40 **The Influence of a New Benzoic Acid Derivative on the Metabolism of Para-Amino Salicylic Acid (PAS) and Penicillin.**
HARRISON F. FLIPPIN, F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania; Visiting Physician, Philadelphia General Hospital; and WILLIAM P. BOGER, F.A.C.P., Assistant Visiting Physician, Philadelphia General Hospital.

3:00 **The Evolution and Treatment of Late Disease of the Liver.**
CHESTER M. JONES, F.A.C.P., Clinical Professor of Medicine, Harvard University.

3:20 INTERMISSION.

Reports from Research Fellows of the College

3:40 **The Effects of Various Physical Procedures on the Circulation in Human Limbs.**
ROBERT W. WILKINS (by invitation), Research Fellow in 1937; Associate Professor of Medicine, Boston University.

4:00 **Hypertension, Systemic and Pulmonary.**
LEWIS DEXTER, F.A.C.P., Research Fellow in 1940; Assistant Professor of Medicine and Tutor in Medicine, Harvard University.

4:20 **A Long Term Study of the Natural History of Essential Hypertension.**
KENNETH A. EVELYN (by invitation), Research Fellow in 1946; Associate Professor of Medicine and Director of the Research Institute of Biophysics, McGill University.

4:40 **Some Clinical Problems of Potassium Metabolism.**
JOHN M. WELLER (by invitation), Alfred Stengel Research Fellow in 1948, Harvard University.

5:00 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered from 9:30 to 11:30 Wednesday and Friday mornings only. They are open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Wednesday, April 19, 1950

Grand Hall, Mechanics' Building

Presiding Officer

William S. McCann, F.A.C.P., Rochester, N. Y.

A.M.

9:30–10:20 **Antibiotics: Yesterday—Today—Tomorrow.**
CHESTER S. KEEFER, F.A.C.P., Wade Professor of Medicine, Boston University.

10:20–10:40 INTERMISSION.

10:40–11:30 **A Diabetic Clinic: Patients with between a quarter and a half century of Diabetes.**
ELLIOTT P. JOSLIN, M.A.C.P., Clinical Professor of Medicine, Emeritus, Harvard University.

Friday, April 21, 1950

Grand Hall, Mechanics' Building

Presiding Officer

William D. Stroud, F.A.C.P., Philadelphia, Pa.

A.M.

9:30–10:20 **Heart Disease: Its Medical Aspects.**
SAMUEL A. LEVINE, F.A.C.P., Clinical Professor of Medicine, Harvard University.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Common Cold and Its Implications.**
WILLIAM J. KERR, F.A.C.P., Professor of Medicine, University of California.

PANEL DISCUSSIONS

Topics of intimate interest and practical value to all members of the profession have been chosen. Qualified men have been selected as leaders and members of the panel personnel. All panels are scheduled from Tuesday through Friday, 12:00 noon to 1:15 P.M., and will be held at Mechanics' Building and the Copley Plaza Hotel.

Applications for tickets to all panels, except those in the Grand Hall of Mechanics' Building, may be made in advance by members on a regular application form which will accompany the final program. Tickets will also be available at the Registration Bureau, Mechanics' Building.

Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS

	Grand Hall Mechanics' Bldg. (Admission by badge; no tickets.)	Paul Revere Hall Mechanics' Bldg. (Admission by ticket only.)	Talbot Hall Mechanics' Bldg. (Admission by ticket only.)	State Suite Copley Plaza Hotel (Admission by ticket only.)	Paul Revere Banquet Hall Mechanics' Bldg. (Admission by ticket only.)
Capacity	3000	450	400	300	230
Tuesday April 18 12:00 M. to 1:15 P.M.	**I** **ACTH and Cortisone—Their Fundamental Implications** Moderator *Walter Bauer Boston *George W. Thorn Boston *Laurance W. Kinsell San Francisco	**II** **Colds, Influenza, and Minor Acute Respiratory Infections** Moderator *Maxwell Finland Boston *Hobart A. Reimann Philadelphia John M. Brewster Philadelphia Francis C. Lowell Boston Norman H. Topping Bethesda *William J. Kerr San Francisco	**III** **Edema** Moderator *Maurice B. Strauss Framingham *Richard H. Lyons Syracuse *Henry A. Schroeder St. Louis Louis G. Welt New Haven	**IV** **Recent Advances in the Treatment of Tuberculosis** Moderator *H. McLeod Riggins New York *John H. Skavlem Cincinnati *Theodore L. Badger Boston	**V** **The Internist as a Psychiatrist** Moderator *Harold G. Wolff New York *Henry M. Thomas, Jr. Baltimore Stewart Wolff New York *Eugene B. Ferris, Jr. Cincinnati Erich Lindemann Boston
	Grand Hall Mechanics' Bldg. (Admission by badge; no tickets.)	Paul Revere Hall Mechanics' Bldg. (Admission by ticket only.)	Talbot Hall Mechanics' Bldg. (Admission by ticket only.)	Sheraton Room Copley Plaza Hotel (Admission by ticket only.)	Paul Revere Banquet Hall Mechanics' Bldg. (Admission by ticket only.)
Capacity	3000	450	400	300	230
Wednesday April 19 12:00 M. to 1:15 P.M.	**VI** **Electrocardiography** Moderator *Samuel A. Levine Boston *George E. Burch, Jr. New Orleans *Franklin D. Johnston Ann Arbor *Francis F. Rosenbaum Milwaukee *Gordon B. Myers Detroit *Charles C. Wolferth Philadelphia	**VII** **Hormonal and Chemotherapy of Cancer** Moderator Charles Huggins Chicago Ira T. Nathanson Boston *C. P. Rhoads New York Sydney Farber Boston Matthew Block Chicago	**VIII** **Management of Syphilis** Moderator J. Earle Moore Baltimore Theodore J. Bauer Washington Charles R. Rein New York Thomas B. Turner Baltimore Augustus R. Rose Boston.	**IX** **Medical Aspects of Atomic Energy—for War and for Peace** Moderator John Z. Bowers Washington G. Failla New York Austin M. Brues Chicago Stafford L. Warren Los Angeles Charles L. Dunham Washington	**X** **Poliomyelitis** Moderator *Conrad Wesselhoeft Boston W. Lloyd Aycock Boston Louis Weinstein Boston Philip M. Stimson New York R. Cannon Eley Boston

*F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Grand Hall Mechanics' Bldg. (Admission by badge; no tickets.)	Paul Revere Hall Mechanics' Bldg. (Admission by ticket only.)	Talbot Hall Mechanics' Bldg. (Admission by ticket only.)	Sheraton Room Copley Plaza Hotel (Admission by ticket only.)	Paul Revere Banquet Hall Mechanics' Bldg. (Admission by ticket only.)
Capacity	3000	450	400	300	230
Thursday April 20 12:00 M. to 1:15 P.M.	**XI** **Surgical Therapy of Cardiovascular Disease** Moderator *C. Sidney Burwell Boston *Lewis Dexter Boston Dwight E. Harken Boston *Johnson McGuire Cincinnati	**XII** **Recent Advances in Antimicrobial Therapy** Moderator (To be announced) *Chester S. Keefer Boston *Maxwell Finland Boston Theodore E. Woodward Baltimore *Harry F. Dowling Washington	**XIII** **Anemia in the Light of Recent Developments** Moderator *William B. Castle Boston Clement A. Finch Seattle *Lawrence E. Young Rochester, N. Y. *Frank H. Bethell Ann Arbor Irving M. London New York	**XIV** **Therapy of Ulcerative Colitis** Moderator *T. Grier Miller Philadelphia Erich Lindemann Boston *Thomas E. Machella Philadelphia Franz J. Ingelfinger Boston Thomas P. Almy New York Bentley P. Colcock Boston	**XV** **Diabetes** Moderator Allan M. Butler Boston *Jerome W. Conn Ann Arbor *Alexander Marble Boston Henry T. Ricketts Chicago Edward Tolstoi New York
Friday April 21 12:00 M. to 1:15 P.M.	**XVI** **Drug Therapy in Allergic Disease** Moderator *Harry L. Alexander St. Louis Francis C. Lowell Boston Marion B. Sulzberger New York *Samuel M. Feinberg Chicago	**XVII** **Pharmacotherapy of Hypertension** Moderator Robert W. Wilkins Boston Reginald H. Smithwick Boston *Robert D. Taylor Cleveland Gordon K. Moe Ann Arbor	**XVIII** **Therapy of Thyroid Disease** Moderator *Samuel F. Haines Rochester, Minn. *James H. Means Boston *Elmer C. Bartels Boston *Edwin B. Astwood Boston Rulon W. Rawson New York	**XIX** **Fever of Obscure Origin** Moderator *Chester S. Keefer Boston *Charles W. Wainwright Baltimore *Hobart A. Reimann Philadelphia *Howard L. Alt Chicago	**XX** **Management of Acute Renal Insufficiency** Moderator Charles H. Burnett Boston Tracy B. Mallory Boston John P. Peters New Haven I. Snapper New York John P. Merrill Boston

*F.A.C.P.

THE CLINIC SESSIONS

The **Clinics** will be conducted on **Tuesday and Thursday** from 9:15 A.M. to 11:30 A.M., and Morning Lectures will be conducted on Wednesday and Friday mornings. On **Tuesday through Friday mornings** a special feature this year will be a **televised program** from the Massachusetts General Hospital by a group of physicians from participating hospitals within the city. Complete details will be available in the final program. Participating hospitals are listed in the following table, with the days on which they present clinics. While most of these sessions will be held at the respective hospitals as usual, one will be offered at the Quincy Hall, John Hancock Life Insurance Building, and the televised clinics will be received at Mechanics' Building.

Adequate accommodations will be provided for all, but **admission to most of these sessions will require special tickets** which will be issued to members in advance of the Session and to non-members directly at the Registration Bureau in the Mechanics' Building. Application forms for tickets for the clinics will accompany the final program to all members.

Emphasis will be placed on clinics in the true sense of that term—that is, patients will be shown and discussed rather than having presentation of formal short papers.

SCHEDULE OF COLOR TELEVISION PROGRAMS

Basement Floor, below Grand Hall, Mechanics' Building

(Starting at 10:00 A.M., daily)

	Duration of Clinic in Minutes	
Tuesday, April 18, 1950		
Tumor Patients—Dr. Joseph C. Aub	20	MGH
Neurological Physical Examination—Dr. Stanley Cobb	15	MGH
Cation Exchange Resin in Donor Blood—Dr. Charles Emerson	10	MMH
Gastroscopy—Dr. Seymour J. Gray	15	PBBH
Shunt Operation for Mitral Stenosis—Dr. Edward F. Bland	20	MGH
Erythema Nodosum—Dr. Cutting B. Favour	10	PBBH
Pemphigus—Dr. Chester Frazier	15	MGH
	105	
Wednesday, April 19, 1950		
Skin Patients—Dr. John G. Downing	20	BCH
Hemochromatosis—Dr. Thomas A. Warthin	10	RVH
Liver Patients—Dr. Chester M. Jones	15	MGH
Neurological Patients—Dr. Stanley Cobb	20	MGH
Localized Myxedema—Dr. Thomas A. Warthin	10	RVH
Orbitonometry—Dr. James H. Means	15	MGH
Congenital Methemoglobinemia—Drs. Ernest Craige and Frank H. Gardner	15	MGH / PBBH
	105	
Thursday, April 20, 1950		
Neurological Patients—Dr. Derek Denny-Brown	20	BCH
Liver Biopsy—Dr. Chester M. Jones	20	MGH
Iliac Crest Biopsy—Dr. Frank H. Gardner	10	PBBH
Peripheral Vascular Disease—Peripheral Vascular Service	15	MGH
Diseases of the Eye—Eye Service	20	MEEI
Endocrine Treatment of Malignancy—Tumor Clinic	20	MMH
	105	

Friday, April 21, 1950

Diabetic Gangrene—Dr. Howard Root	10	NEDH
Neuropsychiatric Patients—Dr. Augustus S. Rose	20	BPH
ACTH in Rheumatic Fever—Dr. Benedict F. Massell	10	HGS
ACTH in Rheumatoid Arthritis—Dr. Theodore B. Bayles	10	RBBH
Spinal and Sternal Biopsy—Dr. William C. Moloney	15	BCH
Endocrine Patients—Dr. Nathan Talbot	20	MGH
X-Ray vs. Pathology Contest—Drs. Merrill Sosman, Richard Schatzki, and Ronald Sniffen	20	PBBH MAH MGH
	105	

Key:

BCH—Boston City Hospital
BPH—Boston Psychopathic Hospital
HGS—House of the Good Samaritan
MAH—Mt. Auburn Hospital
MEEI—Massachusetts Eye and Ear Infirmary
MGH—Massachusetts General Hospital
MMH—Massachusetts Memorial Hospitals
NEDH—New England Deaconess Hospital
PBBH—Peter Bent Brigham Hospital
RBBH—Robert Breck Brigham Hospital
RVH—W. Roxbury Veterans Administration Hospital

SUMMARY OF HOSPITAL CLINICS

Tuesday and Thursday Mornings
April 18 and 20, 1950

	HOSPITALS	TUESDAY	THURSDAY
A	Beth Israel Hospital	Clinic	Clinic
B	Boston City Hospital	Clinic	Clinic
C	Peter Bent Brigham Hospital	Clinic	Clinic
D	Robert Breck Brigham Hospital	Clinic	Clinic
E	Lahey Clinic*	Clinic	Clinic
F-1	Massachusetts Memorial Hospitals	Clinic	Clinic
F-2	Massachusetts Memorial Hospitals, Haynes Memorial, Brighton	Clinic	
G	Pratt Diagnostic Hospital & New England Center Hospital	Clinic	Clinic
H	New England Deaconess Hospital	Clinic	Clinic
J	Veterans Administration Hospital, West Roxbury	Clinic	
K	Veterans Administration Hospital, Framingham		Clinic

* This clinic will be held at Dorothy Quincy Hall, John Hancock Life Insurance Building. All other clinics will be held at the hospitals indicated.

PROGRAM OF CLINICS

Tuesday, April 18, 1950

A BETH ISRAEL HOSPITAL

(330 Brookline Avenue)

(Capacity, 180)

9:15 Some Aspects of Hemorrhagic Diseases.
Benjamin Alexander.

10:15 Further Observation on the Wolff-Parkinson-White Syndrome.
Louis Wolff.

B BOSTON CITY HOSPITAL

(818 Harrison Avenue)

(Capacity, —)

9:15 The Physiological Study of Chronic Emphysema Treated with Pneumoperitoneum.
Edward A. Gaensler.

9:40 The Management of the Patient in Status Asthmaticus.
Maurice Segal.

10:00 Polycythemia.
William B. Castle.

10:20 Treatment of Multiple Myeloma with Urethane.
William C. Moloney.

10:50 From the Department of Dermatology and Syphilology: Diagnosis and Treatment of Common Skin Diseases and Latest Methods of Treating Syphilis.
John G. Downing.

C PETER BENT BRIGHAM HOSPITAL

(721 Huntington Avenue)

(Capacity, 200)

ENDOCRINOLOGY AND METABOLISM

George W. Thorn, presiding

9:15 The Management of Thyroid Disease.
George W. Thorn.
Francis D. Moore.

9:55 The Clinical Use of Cation Exchange Resins in the Treatment of Edema.
Kendall Emerson.

10:15 The Clinical Use of ACTH and Cortisone.
Peter Forsham.

10:35 The Treatment of Uremia by External Dialysis.
John Merrill.

D ROBERT BRECK BRIGHAM HOSPITAL

(125 Parker Hill Avenue)

(Capacity, 100)

9:15 The Medical Management of Rheumatoid Arthritis.
Victor G. Balboni.

9:55 Observations on ACTH and Cortisone in Rheumatoid Arthritis.
Theodore B. Bayles.

10:45 Rheumatoid Spondylitis (Marie-Strümpell Arthritis) Orthopedic Management.
Theodore A. Potter.

E LAHEY CLINIC

Clinic at Dorothy Quincy Hall,

John Hancock Life Insurance Company Building

(Capacity, 400)

9:15 Marie-Strümpel Arthritis.
Frank P. Foster.

9:30 Ambulatory Anticoagulant Therapy.
James A. Evans.

9:45 Hypersplenism.
John W. Norcross.

10:00 Hyperinsulinism.
Frank N. Allan.

10:30 Hypopituitarism.
Lewis M. Hurxthal.

10:45 Hypermetabolism.
Elmer C. Bartels.

11:15 Cancer of the Lung.
Carleton R. Souders.

F-1 MASSACHUSETTS MEMORIAL HOSPITALS

(750 Harrison Avenue)

(Capacity, 80)

9:15 The Diagnosis and Treatment of Pheochromocytoma.
Robert W. Wilkins.
Reginald H. Smithwick.

10:15 The Diagnosis and Treatment of Bronchial Asthma.
Francis C. Lowell and Associates.

F-2 **MASSACHUSETTS MEMORIAL HOSPITALS**

HAYNES MEMORIAL

(Brighton)

(Capacity, 50)

9:30–11:15 Infectious Diseases of the Nervous System.
Louis Weinstein.

G **JOSEPH H. PRATT DIAGNOSTIC HOSPITAL**

and

NEW ENGLAND CENTER HOSPITAL

(30 Bennet Street)

(Capacity, 125)

9:15 Xanthomatosis: A Clinical Demonstration.
Siegfried J. Thannhauser.

9:45 Renal Failure.
Robert P. McCombs.

10:15 Cardiac Pain: The Problem of Classification.
Samuel Proger.

10:45 Spleen and Hypersplenism.
William Dameshek.

H **NEW ENGLAND DEACONESS HOSPITAL**

(16 Deaconess Road)

(Capacity, 75)

Elliott P. Joslin, presiding

9:15 Problems in the Diagnosis of Diabetes.
Alexander Marble.

9:45 Treatment of Diabetes with Diet and Insulin.
Howard F. Root.

10:15 Diabetes Complicating Pregnancy.
Priscilla White.

10:45 Serious Silent Lesions of the Chest.
Richard H. Overholt.

J

VETERANS ADMINISTRATION HOSPITAL

(West Roxbury, Mass.)

(Capacity, 150)

Richard P. Stetson, presiding

9:15 The Combined Management of Upper Gastrointestinal Tract Hemorrhage.
Thomas A. Warthin.
Richard Warren.
Agon Wissing.

9:45 The Diagnosis of Angina Pectoris.
David Littmann.
Melvin Rodman.

10:05 New Methods in the Diagnosis of Infection with Schistosomiasis Japonicum and Other Parasitic Diseases.
Donald Augustine.
Thomas A. Warthin.

10:20 The Treatment Failure of Subacute Bacterial Endocarditis.
David Littmann.
Roy Schaff.

10:45 Treatment of Panhypopituitarism.
Edwin Peterson.

Thursday, April 20, 1950

A

BETH ISRAEL HOSPITAL

(330 Brookline Avenue)

(Capacity, 180)

9:15 The Treatment of Thyrotoxicosis.
Samuel L. Gargill.
Mark F. Lesses.

10:15 Radioactive Iodine in Intractable Angina Pectoris and Congestive Failure.
A. Stone Freedberg.

B

BOSTON CITY HOSPITAL

(818 Harrison Avenue)

(Capacity, —)

9:15 Certain Neurological Complications of General Medical Diseases.
Derek Denny-Brown.

9:40 Antibiotic Therapy.
Maxwell Finland.

10:05 Khellin in the Treatment of Angina Pectoris.
Kermit H. Katz.
Harold L. Osher.

10:25 The Surgical Treatment of Mitral Stenosis.
Dwight E. Harken.

10:50 Psychosomatic Disturbances of Ophthalmic Origin.
James J. Regan.

C PETER BENT BRIGHAM HOSPITAL

(721 Huntington Avenue)

(Capacity, 200)

CARDIOVASCULAR DISEASE

C. Sidney Burwell, presiding

9:15 X-Ray Conference—Heart Disease.
Samuel A. Levine.
Merrill Sosman.

9:55 Mitral Stenosis—Clinical and Physiological Correlation.
Lewis Dexter.

10:15 Constrictive Pericarditis.
Eugene C. Eppinger.

10:35 Venous Pressure in Diagnosis.
C. Sidney Burwell.

D ROBERT BRECK BRIGHAM HOSPITAL

(125 Parker Hill Avenue)

(Capacity, 100)

9:15 The Life History of Juvenile Rheumatoid Arthritis.
Robert E. Barkin.

9:45 Observations on ACTH and Cortisone in Juvenile Rheumatoid Arthritis.
J. Sydney Stillman.

10:25 Orthopedic Management of Rheumatoid Arthritis: Hands and Shoulders.
Robert S. Hormell.

10:55 Orthopedic Management of Rheumatoid Arthritis: Feet and Knees.
John G. Kuhns.

E LAHEY CLINIC

Clinic at Dorothy Quincy Hall,

John Hancock Life Insurance Company Building

(Capacity, 400)

9:15 Clinical Effect of Splanchnicectomy on Gastrointestinal Tract.
John R. Ross.

9:35 Diagnosis of Colonic Lesions.
Martin L. Tracey.

9:55 Chronic Relapsing Pancreatitis.
Francis E. McDonough.

10:15 Regional Ileitis.
Everett D. Kiefer.

10:35 Strictures of Common Bile Duct.
S. Allen Wilkinson.

10:55 Complicated Peptic Ulcer.
Sara M. Jordan.

F-1 MASSACHUSETTS MEMORIAL HOSPITALS

(750 Harrison Avenue)

(Capacity, 80)

9:15 The Diagnosis of Pancreatic Disease.
Franz J. Ingelfinger.
Henry M. Lemon.

10:15 Radiophosphorus Treatment of Leukemia.
Joseph F. Ross and Associates.

G JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

and

NEW ENGLAND CENTER HOSPITAL

(30 Bennet Street)

(Capacity, 125)

9:15 Clinical Thyroid Disease.
Edwin B. Astwood.

9:45 Neurological Clinic.
Raymond D. Adams.

10:15 ACTH—Clinical and Biochemical Observations.
Freddy Homburger.

10:45 Correlation of Clinical and Roentgenological Studies in Gastrointestinal Diseases.
Alice Ettinger.

H NEW ENGLAND DEACONESS HOSPITAL

(16 Deaconess Road)

(Capacity, 75)

Howard F. Root, presiding

9:15 Diabetic Coma and Its Treatment.
Alexander Marble.

9:45 Clinico-Pathological Demonstration: Vascular Disease in Young Diabetics.
Howard F. Root.
Shields Warren.

10:15 New Aspects of Diabetic Surgery Including Transmetatarsal Amputation.
Leland S. McKittrick.

10:45 The Future of the Diabetic.
Elliott P. Joslin.

K CUSHING VETERANS ADMINISTRATION HOSPITAL

(Framingham, Mass.)

(Capacity, 200)

9:30 Acute Benign Pericarditis.
Morton G. Brown.

9:50 Graves' Disease: Treatment with I-131.
Joseph F. Ross.
Arthur A. Hagelstein.

10:10 Pheochromocytoma.
Maurice B. Strauss.
Robert O. Oseasohn.

10:30 Acromegaly: Endocrine Treatment.
Jack D. Rosenbaum.
Robert K. Davis.

10:50 Cardiac Aneurysm.
Daniel Holzman.

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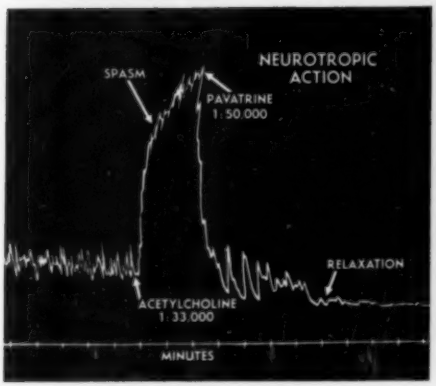
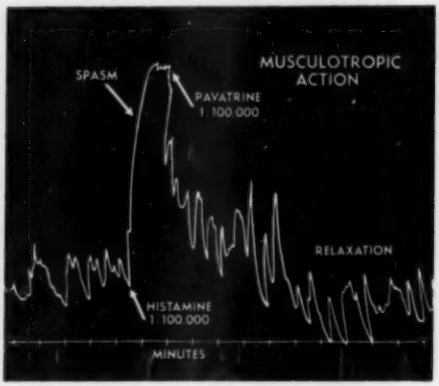


Neurotropic Action: Excised rabbit uterus contracted with acetylcholine and relaxed with Pavatrine.



Musculotropic Action: Excised rabbit uterus contracted with histamine and relaxed with Pavatrine.

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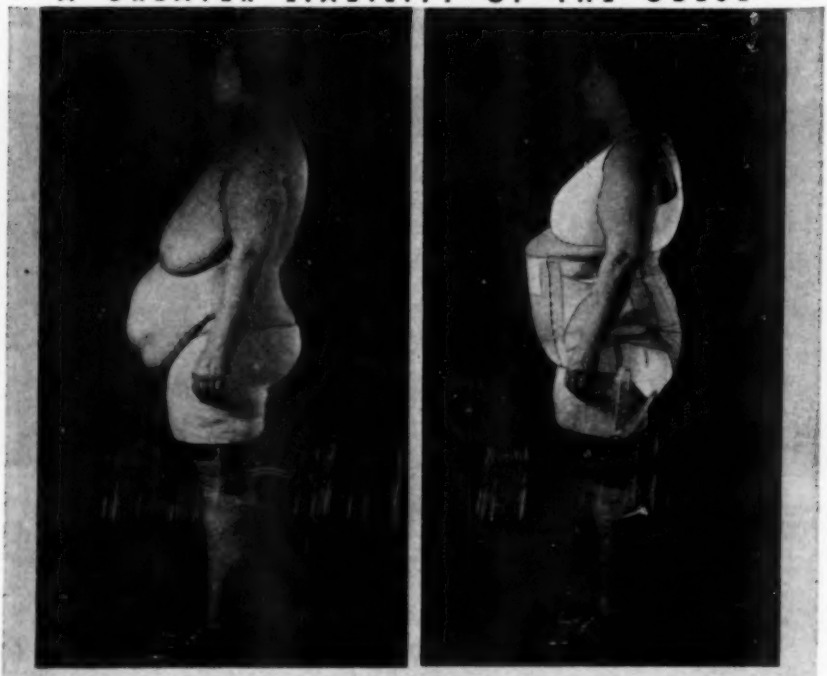

● Photograph of patient, 51 years old. Weight — 226 lbs.; height — 5 ft. 5 in.

Patient was operated four years ago for fibroid tumors of the uterus when weighing 240 lbs. Complete disruption of the wound occurred on the fourth day. Pneumonia followed, requiring a six month's stay in the hospital.

● Photograph of patient after application of support.

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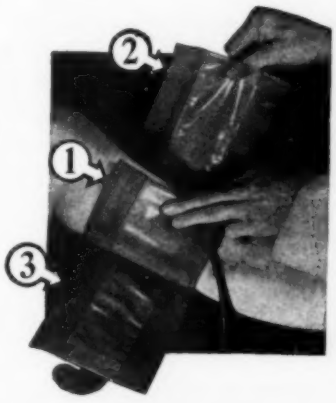

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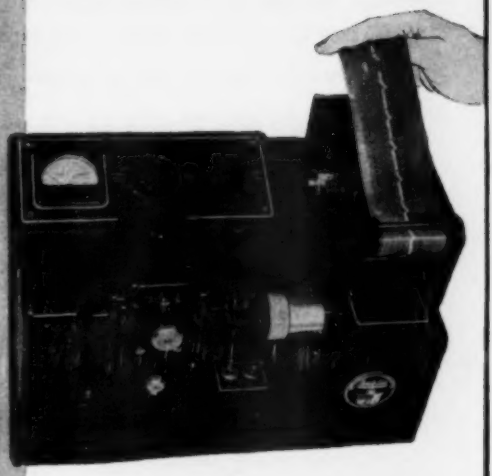

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